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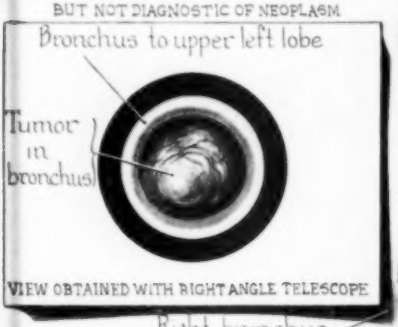

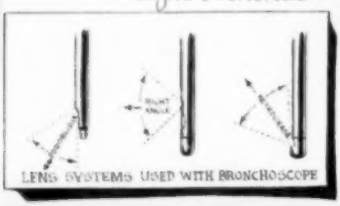

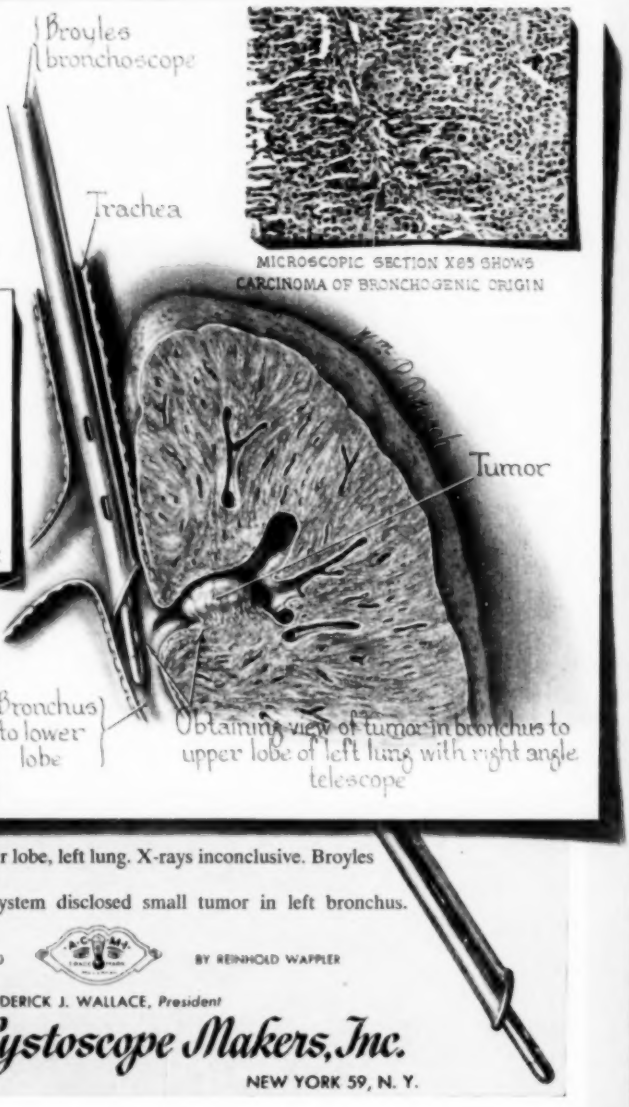
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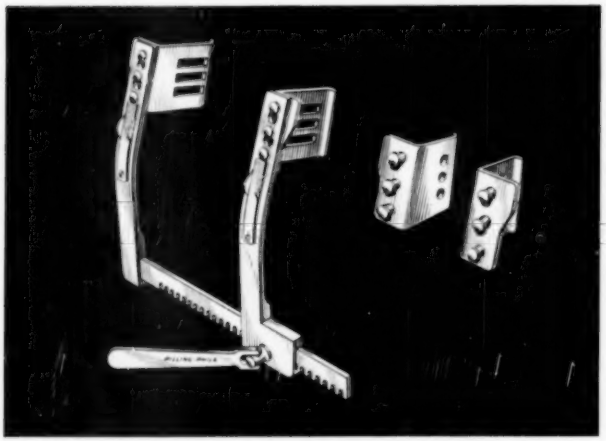

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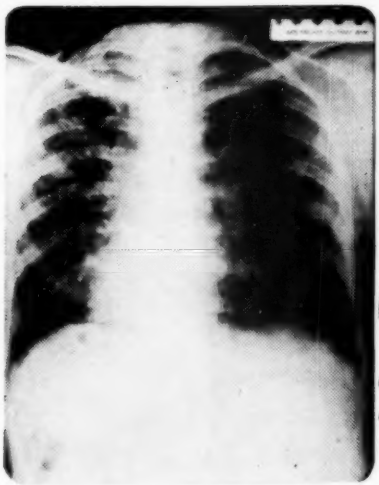

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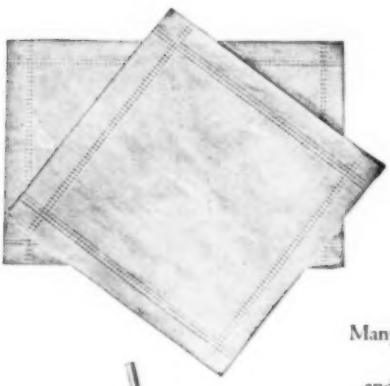

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THE AMERICAN REVIEW
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VOLUME 62 *November 1950* NUMBER 5

BCG VACCINATION IN SILICOSIS[1, 2, 3]

A. J. VORWALD, M. DWORSKI, P. C. PRATT, AND A. B. DELAHANT

(Received for publication April 26, 1950)

INTRODUCTION

Although there is still some controversy concerning the effectiveness of immunization with vaccine of the Bacillus Calmette-Guerin, many recent studies (1, 2, 3, 4) on BCG vaccination indicate an appreciable reduction in tuberculosis affecting certain groups of people who may have had an unusual exposure to the disease, a low resistance, or both. It has been definitely established both experimentally (5, 6, 7) and clinically (8) that the inhalation of crystalline free silica decreases resistance to pulmonary tuberculosis. In this country approximately 65 per cent of the silicotics who come to autopsy show evidence of active tuberculosis. In contrast, industrial workers without silicosis, but exposed to nonsilicious dust, have an incidence of only 15 per cent of tuberculous disease (9). It would seem logical that the high incidence might be lowered by BCG vaccination of tuberculin-negative individuals exposed to an unavoidable silica hazard. Before considering the clinical application of such vaccination, however, and in view of our knowledge of the effect of silica on infection produced by the attenuated strain R_1 of human-type tubercle bacillus (6), it became necessary first to observe the course of infection with the BCG organisms in animals inhaling silica. Therefore, the following experiments were designed and initiated concurrently:

I. To determine the course of the tuberculous infection produced by the *intracutaneous* injection of BCG organisms in guinea pigs simultaneously exposed by inhalation to atmospheric quartz dust of high concentration.

II. To determine the course of the pulmonary tuberculous infection produced by the *inhalation* of BCG organisms in guinea pigs simultaneously exposed to the inhalation of a high concentration of quartz dust.

[1] From the Saranac Laboratory of The Trudeau Foundation, Saranac Lake, New York.

[2] Presented before the Medical Session, as part of the symposium on *Nontuberculous Diseases of the Chest and Related Matters* at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 26, 1950.

[3] This project was supported by the Biological Sciences Division, Office of Naval Research, U. S. Navy Department, Washington, D. C.

III. To determine the course of the pulmonary tuberculous infection produced by the *inhalation* of BCG organisms in guinea pigs previously exposed for four months by inhalation to atmospheric quartz dust of high concentration, then infected, and continued in the exposure to quartz dust during the development of the tuberculosis.

IV. To determine the degree of protection afforded by BCG vaccination in a developing tuberculosilicosis. The guinea pigs were vaccinated intracutaneously with BCG organisms. At the end of two months, when hypersensitivity to tuberculin had developed, all of the vaccinated animals were infected by *inhalation* with the attenuated R_1 strain of human-type tubercle bacillus, and then were continuously exposed by inhalation to atmospheric quartz dust.

Materials and Methods

Preparation of BCG suspensions and method of infection: The BCG strain employed in these experiments was derived from a culture, strain 826L, supplied by Dr. Sol Roy Rosenthal, Medical Director, Research Foundation, Tice Laboratories, Chicago, Illinois. The original culture was subcultured on glycerolated-water—potato medium. At the end of two weeks' incubation, the film growth on the fluid portion of the medium was transferred to a flask of Sauton's medium. After twelve days' incubation, the surface film was used in preparing the bacterial suspension for intracutaneous inoculation. The surface bacterial film was placed between sterile pads of blotting paper to remove excess moisture. The dried film was weighed and then triturated in a sterile mortar with pestle in a diluent consisting of one part of Sauton's medium and three parts of 0.85 per cent NaCl. Sufficient diluent was added to make a final concentration of 1 mg. of BCG per ml. A volume of 0.1 ml. of this suspension, equivalent to 0.1 mg. of BCG, was used for the intracutaneous inoculation into the left flank of the animals.

For the inhalation infection, a portion of the surface film from a twelve-day culture on Sauton's medium was ground in a sterile mortar with pestle and then diluted with 0.85 per cent NaCl solution. The suspension was centrifuged at low speed for three minutes and then filtered and re-filtered through sterile filter paper until a stained smear from the filtrate showed 30 to 35 bacilli and a very occasional small clump per oil immersion field. The final filtrate was placed in a DeVilbiss atomizer and the animals were infected by a spray produced by twelve puffs from the atomizer given during a period of one minute. Complete details for inhalation infection are described in a previous publication from this laboratory (10).

Method of dust exposure: The methods for exposing animals to quartz dust inhalation have been described in detail in other publications (11). Briefly, the technique consists of exposing the animals to a cloud of the fine quartz particles disseminated in the air of a room by mechanical devices designed to produce the desired dispersion and concentration of particles in the atmosphere. Samples of the atmospheric dust were collected from time to time with a Greenburg-Smith impinger apparatus. Study of these samples revealed that the atmospheric concentration of the dust was approximately 500 million particles per cubic foot of air. An analysis of the size distribution of the particles showed that more than 99 per cent were less than 10 microns in diameter. Chemical analysis showed a total silica content greater than 99 per cent. The animals in all of these experiments were exposed to the dust eight hours daily, six days a week.

TABLE 1

Experiment I

INTRACUTANEOUS BCG AND QUARTZ INHALATION SIMULTANEOUSLY					CONTROLS INTRACUTANEOUS BCG				
Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes	Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes
		months					*months*		
1	K	2	0	1	51	K	2	0	0
2	K		0	1	52	K		+	0
3	K	4	0	2	53	K	4	0	0
4	K		0	2	54	K		0	0
5	K	6	0	3	55	K	6	0	1
6	K		0	3	56	K		0	1
7	K	8	+	3	57	K	8	0	1
8	K		0	3	58	K		0	1
9**	K	10	+++	3	59	K	10	0	1
10*	K		+++	3	60	K		0	1
11	K	12	0	2	61	K	12	0	2
12	K		++++	3	62	K		0	2
19	D	13½	++++	3					
13	D	13½	+++	3					
16	D	13⅔	++++	3					
18*	D	14	++++	3	63*	K	14	0	1
14**	K		0	3	64**	K		0	2
15**	K		0	3					
17**	D	15½	++++	3					
20**	K	16	0	3	65*	K	16	++	3
25**	K		0	3	66	K		0	3
21**	K	18	++	3	67**	K	18	0	0
22*	K		++	3	69*	K		0	1
23**	K		++	3					
24**	K		0	3					

Key: K = Killed for sampling
D = Died
* = Organisms isolated
** = No organisms isolated

Lungs: 0 = No recognizable tubercles
\+ = Recognizable nonspreading tubercles
++ = Isolated spreading tubercles
+++ = Isolated spreading tubercles with coalescence
++++ = Extensive areas of coalescent tuberculous lesions.

Enlargement of Tracheobronchial Lymph Nodes:
0 = None
1 = Slight
2 = Moderate and firm
3 = Marked and fibrocaseous

EXPERIMENTAL PROCEDURES AND RESULTS

Experiment I: A group of 25 healthy adult guinea pigs was infected intracutaneously in the left flank with 0.1 ml. of the BCG suspension and was then

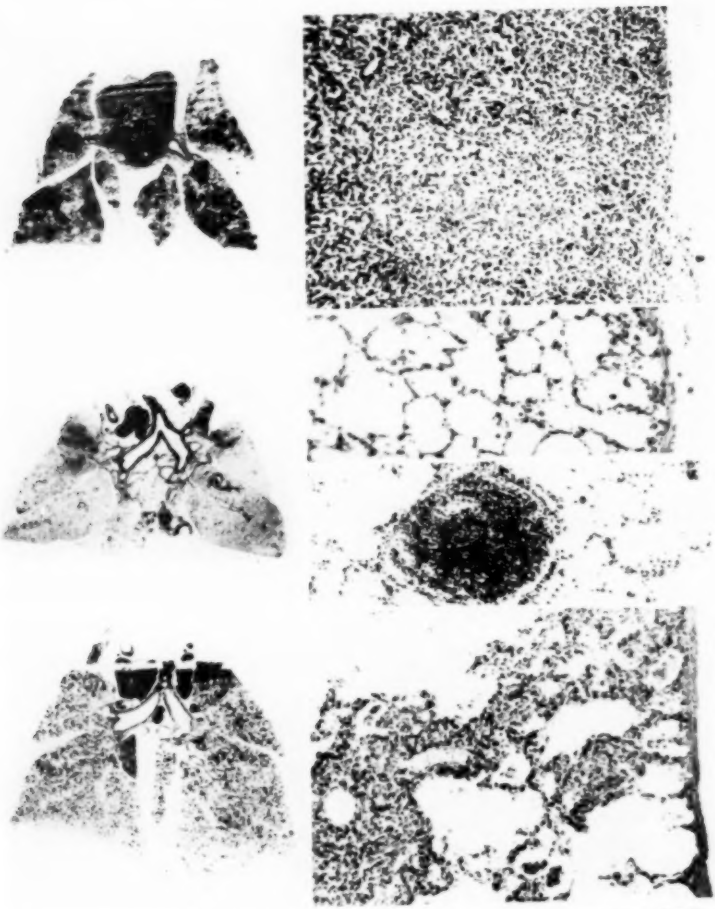

FIG. 1. (Upper left) Experiment I. Guinea Pig Number 10. Intracutaneous BCG plus inhaled quartz. Killed at ten months. The gross section exhibits large coalesced lesions of tuberculosilicosis. The tracheobronchial lymph node is greatly enlarged with central area of caseation. (1.5×)

FIG. 2. (Upper right) Photomicrograph of a subpleural area of tuberculosilicosis in the lung shown in figure 1. The pleural surface is at the right. There is dense infiltration with macrophages, lymphocytes, and fibrocytes distorting and destroying the pulmonary structure. There is a necrotizing focus just below the center, surrounded by a zone of epithelioid cells. (150×)

FIG. 3. (Center left) Experiment I. Guinea Pig Number 59. Intracutaneous BCG control. Sacrificed at ten months. The gross section reveals the lungs to be generally air-containing and essentially normal. The scattered dark foci consist of lymphoid tissue, which is frequently seen in otherwise normal lungs. (1.5×)

exposed by inhalation to atmospheric quartz dust of high concentration as previously described. A control group of 18 healthy guinea pigs was infected in like manner and kept in normal air. All animals were skin tested with Old Tuberculin (OT) at six weeks after infection and at four-month intervals thereafter. Skin reactions with areas of erythema and induration varying from 14 to 20 mm. in diameter were elicited in all animals. Some showed central areas of necrosis varying in size up to 8 mm. in diameter. Another control group of 25 healthy guinea pigs was exposed to quartz dust but was not infected with BCG. It may be said here that these animals developed silicosis in the usual manner during the eighteen-month course of the experiment. It may be said further that not a single member of this group developed any evidence of tuberculous infection (figures 5, 6, 13, and 16).

The animals infected intracutaneously with BCG developed at the eighth to tenth day at the site of inoculation an indurated nodule varying from 5 to 8 mm. in diameter and 1 to 2 mm. in thickness. The skin over the indurated area ulcerated at about the fourteenth day and a small scale formed over the nodule. There was no deep necrosis and caseation with discharge was not noted. At the end of two months the lesion was completely healed; a small scar indicating the site of injection in most animals, the remainder revealing no evidence of the injection. The draining inguinal and para-iliac lymph nodes on the homolateral side were slightly to moderately enlarged at two and at four months. At six months these nodes were small and appeared normal in the gross, being no different from those on the contralateral side.

The progress of this experiment was observed by sacrificing 2 animals at two-month intervals. Two control animals also were killed at the same time. The gross tuberculous pulmonary findings are detailed in table 1 and summarized in table 6. At this point it may be stated that microscopic sections have been prepared from lungs, spleen, liver, and tracheobronchial and hepatic lymph nodes of all animals to confirm gross findings.

The animals were observed over a period of eighteen months. Animals killed up to ten months showed no evidence of gross spreading disease in the lungs, although during this period the tracheobronchial lymph nodes steadily increased

FIG. 4. (Center right upper half) Photomicrograph of a subpleural area of the lung shown in figure 3. The structure is normal. Note the presence of an occasional intra-alveolar phagocytic cell. (150×) (Center right lower half) Photomicrograph of a focus of lymphoid tissue in the lung shown in figure 3. (150×)

FIG. 5. (Lower left) Experiment I. Guinea Pig Number 112. Quartz inhalation only. Sacrificed at ten months. The gross section reveals numerous dark foci. The general appearance should be contrasted with that in figure 1. The rather uniform small size, the isolation of lesions, and the absence of wide zones of pleural involvement serve to distinguish the simple silicotic foci from the tuberculosilicotic lesions demonstrated in figure 1. (1.5×)

FIG. 6. (Lower right) Photomicrograph of a subpleural area of the lung shown in figure 5. The appearance is to be contrasted with that in figure 2. The preservation of lung structure, with macrophages in the alveolar spaces and walls, the absence of epithelioid cells and necrosis, and the slight involvement immediately beneath the pleura serve to distinguish this reaction from the tuberculosilicotic. At the left is a perivascular localization of the dust cells. (150×.)

in size and firmness. The animals killed at ten months did show spreading foci of tuberculosilicosis involving both the lungs and nodes (figures 1 and 2). At thirteen to fifteen months, 5 deaths occurred from advanced tuberculosilicosis and in one animal a marked cavitation was present (figures 7 and 8). Spreading disease

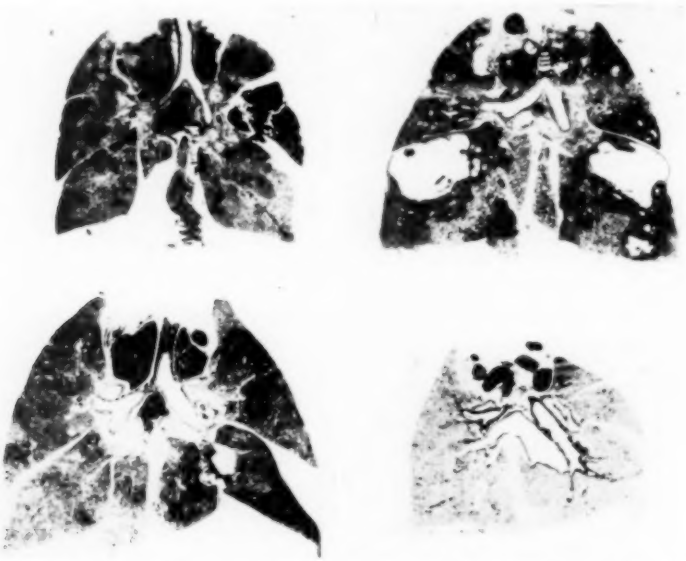

FIG. 7. (Upper left) Experiment I. Guinea Pig Number 18. Intracutaneous BCG plus quartz inhalation. Died at fourteen months. Note the extensive confluent involvement, with obliteration of pulmonary structure and pronounced enlargement of the tracheobronchial lymph nodes. (1.5×)

FIG. 8. (Upper right) Experiment I. Guinea Pig Number 19. Intracutaneous BCG plus quartz inhalation. Died at thirteen months. Note again the extensive involvement as in figure 7, with, in this animal, cavity formation in both caudal lobes. (1.5×)

FIG. 9. (Lower left) Experiment II. Guinea Pig Number 42. Inhalation of BCG plus quartz inhalation. Killed at sixteen months. There is extensive involvement of both lungs which may be compared with the lesions in figures 1, 7, and 8. (1.5×)

FIG. 10. (Lower right) Experiment II. Guinea Pig Number 100. BCG inhalation only. Killed at sixteen months. The lung is essentially normal. The tracheobronchial lymph nodes are but slightly enlarged. (1.5×)

was also found in later sacrificing periods. In all of these experiments the non-silicotic control animals with one exception showed no spreading tuberculous disease (figure 3.) Nevertheless, acid-fast bacilli were isolated by culture of tissue from 3 of 5 animals. The exceptional animal showed two isolated foci of spreading tubercles in the lung and in the spleen. Subinoculations of the organisms isolated from this animal revealed them to be similar in attenuation to the original BCG strain. In contrast to the conglomerate lesions present in the tuberculo-

silicotic group, the uninfected silicotic control animals exhibited scattered fibrocellular lesions which remained discrete (figures 5, 6, 13, and 16).

Acid-fast bacilli were isolated in cultures from the lungs and tracheobronchial nodes from 3 of 12 tuberculosilicotic animals and from 3 of 5 BCG controls (table 8). The method of isolation was as follows: Portions of lung and tracheobronchial lymph nodes were crushed in a sterile mortar with a small amount of sterile sand and physiologic saline; the mixture was transferred to a test tube and allowed to stand for five minutes for settling of the sand and crushed tissue; the supernatant fluid was withdrawn and digested with an equal quantity of 4 per cent sodium hydroxide solution at 37° C. for thirty minutes; after centrifuging the digested fluid, the sediment was neutralized with hydrochloric acid and seeded on three tubes of American Trudeau Society potato-egg medium. Cultures were retained for two months before they were considered negative. The gross growth characteristics of the positive cultures appeared similar to the BCG culture originally employed.

During the course of this experiment, virulence tests were initiated because of the unexpected finding of spreading pulmonary tuberculosilicosis in animals at ten months after infection. The virulence tests of the organisms isolated by culture were made in the following manner: A group of 4 guinea pigs was injected subcutaneously in the right groin with 10 mg. of the growth. The experiment was designed so that one animal of each group could be sacrificed at one, two, four, and eight months after inoculation. Thus, 24 subinoculated animals were being utilized for determining virulence in this particular experiment. Those sacrificed at one and two months showed a subcutaneous abscess at the site of inoculation with slight enlargement and moderate induration of the homolateral inguinal and para-iliac nodes. At four months, the subcutaneous abscess was healed and the nodes were only slightly enlarged. In no instance was there evidence of spread of disease to the viscera. There was no spread in spite of the quantity, 10 mg. of inoculum, which was sufficient to cause progressive disease and death of the animals if the strain had been virulent. The results of these virulence tests will be reported more fully in a separate communication.

From the above findings it is evident that the BCG organisms leave the intracutaneous site of injection in some, if not in all, of the guinea pigs and are carried to the lungs and tracheobronchial nodes, where they remain viable for periods at least as long as eighteen months. Such seedings of the organism in tissue damaged by the presence of quartz dust cause a spreading and fatal tuberculous disease not unlike that demonstrated many times with the attenuated R_1 strain of the human tubercle bacillus (6). Further, the BCG organism isolated from the tuberculosilicotic lesions shows no enhancement of virulence when subinoculated into healthy animals. Thus, the progressive disease is due to a factor of increased tissue susceptibility rather than to any acquired virulence of the infecting organism.

Experiment II: In this experiment 25 healthy adult guinea pigs were given the BCG infection by the inhalation route and were immediately exposed for eight hours daily to atmospheric quartz dust of high concentration averaging 500

million particles per cubic foot of air. A control group of 18 animals was infected in like manner with the same suspension and kept in normal air. Two animals from each group were sacrificed at two-month intervals and examined grossly and microscopically. The results are tabulated in table 2 and summarized in table 6. Again progressive and fatal tuberculosilicotic disease occurred in the silicotic animals infected with the BCG organisms (figure 9). However, in this instance the disease did not become manifest until thirteen months after infection, and deaths occurred later than in Experiment I. The difference in the time of appearance of the progressive disease in the lungs between Experiment I and Experiment II may presumably be explained by the theory that in the former experiment the lung was more heavily seeded by BCG organisms drained from the intracutaneous localization of the bacilli than by the organisms implanted directly in the lung by inhalation of the atomized spray containing the BCG organisms, as occurred in Experiment II.

The BCG control animals remained free of pulmonary tuberculosis (figure 10). The tracheobronchial lymph nodes, however, in some of the BCG control animals were enlarged. The silicotic control animals exhibited scattered isolated lesions in the lungs with enlargement and hyalinization of the tracheobronchial nodes, changes which are characteristic of uncomplicated silicosis in the experimental guinea pig. These characteristic isolated lesions are in contrast to the conglomerate disease present in the silicotic group complicated by BCG infection.

Virulence tests were conducted as described for Experiment I. Referring to table 8, it will be noted that cultures were obtained from 4 of 7 tuberculosilicotic animals. These animals, identified in table 2, were sacrificed or died at fourteen, sixteen, and eighteen months. The cultures on subinoculation into guinea pigs have given no evidence of enhanced virulence of the BCG organism itself. In contrast, cultures from the 4 BCG control animals sacrificed at comparable intervals remained negative. The negative findings are interesting in comparison with the isolation of organisms in 3 of 5 animals which were infected by the intracutaneous route. It may be inferred that the relatively few organisms introduced by the inhalation method were destroyed by the fourteenth month. An experiment is now in progress in which attempts are being made to isolate the organism in the earlier months of the infection.

Experiment III: In this experiment, an inhalation infection with BCG organisms was given to 25 healthy adult guinea pigs which had previously been exposed for four months to atmospheric quartz dust of high concentration. Control animals which had not been exposed to dust were similarly infected. The results are given in detail in table 3 and are summarized in table 6. As indicated, spreading disease became manifest in the lungs of the dusted animals as early as two and one-half months after infection, demonstrating in this instance acceleration of disease when bacilli are localized in pulmonary tissue already affected by the reaction to quartz dust. Thus, there was no lag period as was observed in Experiments I and II, where tissue reaction to quartz had not been previously established. During the course of Experiment III, a total of 19 animals exhibited progressive tuberculosilicosis (figures 11 and 14). The disease terminated fatally

TABLE 2

Experiment II

BCG INHALATION AND QUARTZ INHALATION SIMULTANEOUSLY					CONTROLS BCG INHALATION				
Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes	Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes
		months					*months*		
26	K	2	0	1	76	K	2	0	1
27	K		+	1	77	K		0	1
28	K	4	0	1	78	K	4	0	0
29	K		0	1	79	K		0	0
30	K	6	0	3	80	K	6	0	0
31	K		+	3	81	K		0	0
32	K	8	0	3	82	K	8	0	0
33	K		0	3	83	K		0	0
34	K	10	+	3	84	K	10	0	1
35	K		0	3	85	K		0	1
36	K	12	0	3					
37	K		0	3					
					86	K	12	0	1
					87	K		0	1
40	D	13½	0(1)	3					
38	D		++++	3					
50	D	13¾	++	3					
48	D		+++	3					
39*	K	14	++	3	88**	K	14	0	1
41	K		++	3	89	K		0	1
47	D		++++	3					
46*	K	16	++	3	94**	K	16	0	2
49**	K		++	3	100	K		0	2
43**	D	16½	+++	3					
42*	D	16½	++++	3					
44**	D	18	++	3	90**	K	18	0	1
45*	K		++++	3	91**	K		0	1

Key: K = Killed for sampling
D = Died
* = Organisms isolated
** = No organisms isolated
(1) = Pneumonia

Lungs: 0 = No recognizable tubercles
\+ = Recognizable nonspreading tubercles
++ = Isolated spreading tubercles
+++ = Isolated spreading tubercles with coalescence
++++ = Extensive areas of coalescent tuberculous lesions

Enlargement of Tracheobronchial Lymph Nodes:

0 = None
1 = Slight
2 = Moderate and firm
3 = Marked and fibrocaseous

TABLE 3

Experiment III

QUARTZ INHALATION FOR FOUR MONTHS, THEN BCG INHALATION WITH QUARTZ INHALATION CONTINUED					CONTROLS BCG INHALATION				
Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes	Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes
		months					*months*		
126	K	2	+	3	151	K	2	0	1
127	K		+	3	152	K		0	1
134	D	2+	0(1)	2					
129	D	2½	+++	3					
135	D	3½	++	3					
128	K	4	++	3	153	K	4	0	1
136	K		++	3	154	K		0	1
					171	D	4+	0(1)	1
					164	D	4+	0(1)	1
					161	D	5	(1)	1
					155	D	5½	(1)	1
130	K	6	++	3	163	K	6	0	—
131	K		++	3	172	K		0	0
138	D	6+	++(1)	3					
139	D		0	3					
140	D	7⅓	0	3					
132	K	8	++	3	156	K	8	0	0
133	K		+++	3	162	K		0	0
150	D	9	++	3					
141	K	10	++	3	157	K	10	0	0
142*	K		++	3	158	K		0	0
143	D	11¼	+++	3					
144*	K	12	++++	3	160	K	12	0	0
145	K		++++	3					
148**	D	12¼	++++	3					
149*	D		++++	3					
146*	D	13	+++	3					
147*	K	14	++++	3	165**	K	14	0	1
					166**	K		0	1

Key: K = Killed for sampling
D = Died
* = Organisms isolated
** = No organisms isolated
(1) = Pneumonia

Lungs: 0 = No recognizable tubercles
\+ = Recognizable nonspreading tubercles
++ = Isolated spreading tubercles
+++ = Isolated spreading tubercles with coalescence
++++ = Extensive areas of coalescent tuberculous lesions.

Enlargement of Tracheobronchial Lymph Nodes:

0 = None
1 = Slight
2 = Moderate and firm
3 = Marked and fibrocaseous

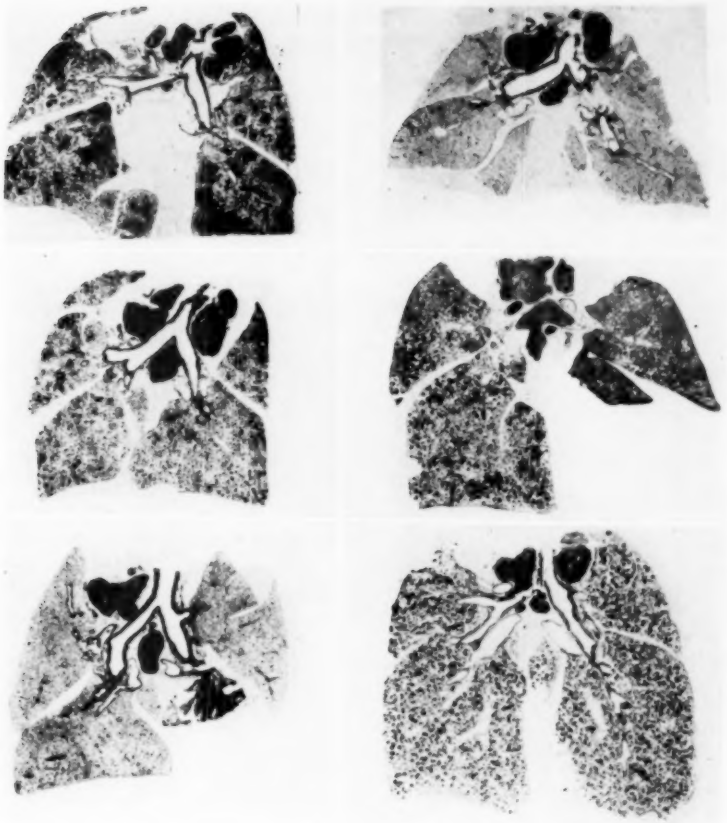

FIG. 11. (Upper left) Experiment III. Guinea Pig Number 133. Quartz inhalation for four months followed by BCG inhalation. Killed eight months after infection. Coalescent areas of tuberculosilicosis are apparent in all lobes. (1.5×)

FIG. 12. (Upper right) Experiment III. Guinea Pig Number 162. BCG inhalation control. Killed at eight months. The lungs are essentially normal. The dark foci consist of lymphoid tissue as in figures 3 and 4 (center right, lower half). The tracheobronchial lymph nodes are but slightly enlarged. (1.5×)

FIG. 13. (Center left) Experiment III. Guinea Pig Number 109. Quartz inhalation control. Killed at twelve months. Note the isolated nodular foci of reaction to the quartz, and contrast with the appearance in figure 11. (1.5×)

FIG. 14. (Center right) Experiment III. Guinea Pig Number 147. Quartz inhalation for four months followed by BCG inhalation. Killed at fourteen months after infection with a total of eighteen months of quartz inhalation. Coalescent areas of tuberculosilicosis are apparent in all lobes. The right caudal lobe was removed for culture. (1.5×)

Fig. 15. (Lower left) Experiment III. Guinea Pig Number 165. BCG inhalation control. Killed at fourteen months. The lungs are essentially normal, with foci of lymphoid tissue as in figure 4 (center right, lower half). The tracheobronchial lymph nodes are but slightly enlarged. The right caudal lobe was removed for culture. (1.5×)

FIG. 16. (Lower right) Experiment III. Guinea Pig Number 120. Quartz inhalation control. Killed at eighteen months. Note the isolated nodular foci of reaction to the quartz, and contrast with the appearance in figure 14. (1.5×)

TABLE 4

Experiment IV

INTRACUTANEOUS BCG, FOLLOWED IN TWO MONTHS BY R_1 INHALATION AND QUARTZ INHALATION					CONTROLS INTRACUTANEOUS BCG FOLLOWED IN TWO MONTHS BY R_1 INHALATION ONLY				
Animal Number	Mode of Death	Time after R_1 Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes	Animal Number	Mode of Death	Time after R_1 Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes
		months					*months*		
176	K	2	+	1	201	K	2	+	1
177	K		+	1	202	K		0	1
178	K	4	+	3	203	K	4	0	2
179	K		+	3	204	K		0	2
193	D	$5\frac{1}{2}$	+	3	215	D	$5\frac{1}{2}$	0(1)	1
180	K	6	++	3	205	K	6	+	1
181	K		++	3	206	K		0	1
					220	D	$6\frac{1}{2}$	0(1)	—
184	D	8	++	3	216	K	8	0	2
196	D		++	3	218	K		0	0
185	K		++++	3					
192	K		+++	3					
189	D	$9\frac{1}{2}$	+++	3	223	D	$9\frac{3}{4}$	0	—
200	D		++++	3					
188	D	$9\frac{3}{4}$	++++	1					
187	D	10	++++	3	224	K	10	0	1
182	K		++++	3	225	K		0	1
183	K		++++	3	208	D	$10\frac{1}{2}$	0	1
199	D		++++	3					
198	D	$10\frac{1}{2}$	++++	3					
186	D	$10\frac{3}{4}$	++++	3					
190	D	$11\frac{1}{4}$	++++	3					
194	D	$11\frac{3}{4}$	++++	3					
191	K	12	++++	3	207	K	12	0	1
195	K		++++	3	209	K		0	1
197	K	14	++++	3	210	K	14	0	1
					211	K		0	1
					212	K		0	1
					213	K		0	1
					214	K		0	1
					217	K		0	1
					218	K		0	1
					221	K		0	1
					222	K		0	1

Key: K = Killed for sampling
D = Died
* = Organisms isolated
** = No organisms isolated
(1) = Pneumonia

Lungs: 0 = No recognizable tubercles
\+ = Recognizable nonspreading tubercles
++ = Isolated spreading tubercles
+++ = Isolated spreading tubercles with coalescence
++++ = Extensive areas of coalescent tuberculous lesions

Enlargement of Tracheobronchial Lymph Nodes:

0 = None
1 = Slight
2 = Moderate and firm
3 = Marked and fibrocaseous

TABLE 5

Experiment V

QUARTZ INHALATION AND R_1 INHALATION INFECTION (CONTROLS OF EXPERIMENT IV)					R_1 INHALATION INFECTION (CONTROLS OF EXPERIMENT IV)				
Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes	Animal Number	Mode of Death	Time after Infection	Tuberculosis of the Lungs	Enlargement of Tracheobronchial Lymph Nodes
		months					*months*		
248	D	2	+(2)	2	259	K	2	+	1
229	D		+(2)	2	261	K		+	1
237	D		+(2)	2					
240	D		+(2)	2					
247	D		+(2)	2	275	D	3	+(1)	1
226	K	4	++	2	251	K	4	+	2
227	K		++	2	252	K		+	2
228	K	6	+++	2	253	K	6	+	2
236	K		+++	2	254	K		+	2
					274	D		0(1)	2
246	K	8	+++	2	255	K	8	0	2
249	K		+++	2	256	K		0	2
					270	D	9½	0(1)	1
231	D	10	++++	1	271	K	10	+	2
230	K		++++	2	272	K		+	2
241	K		+++	2					
239	D		+++	2					
232	D	10½	++++	2					
250	D	11½	++++	2					
242	D	12	++++	2	257	K	12	+	2
233	K		++++	2	258	K		+	2
234	K		++++	2					
244	D	13	++++	2	260	K	14	+	2
238	D		+++	2	262	K		+	2
235	D		++++	2	263	K		+	2
243	D		++++	2	264	K		+	2
245	D	13½	++++	2	265	K		0	2
					266	K		+	2
					267	K		0	2
					268	K		+	2
					269	K		+	2
					273	K		+	2

Key: K = Killed for sampling
D = Died
* = Organisms isolated
** = No organisms isolated
(1) = Pneumonia
(2) = Diarrhea

Lungs: 0 = No recognizable tubercles
\+ = Recognizable nonspreading tubercles
++ = Isolated spreading tubercles
+++ = Isolated spreading tubercles with coalescence
++++ = Extensive areas of coalescent tuberculous lesions.

Enlargement of Tracheobronchial Lymph Nodes:

0 = None
1 = Slight
2 = Moderate and firm
3 = Marked and fibrocaseous

TABLE 6

BCG Infection in Experimental Silicosis in Guinea Pigs

Summary of Data on Gross Pulmonary Tuberculous Disease

EXPERIMENTS	NUMBER OF PIGS	NUMBER OF PIGS SACRIFICED AT INTERVALS			NUMBER OF DEATHS			TOTAL WITH SPREADING DISEASE
		Negative	With non-spreading disease	With spreading disease	Negative	With non-spreading disease	With spreading disease	
Experiment I								
Intracutaneous BCG and quartz inhalation simultaneously	25	13	1	6	0	0	5	11
Controls: Intracutaneous BCG	18	16	1	1	0	0	0	1
Experiment II								
BCG inhalation and quartz inhalation simultaneously	25	9	3	5	1	0	7	12
Controls: BCG inhalation	18	18	0	0	0	0	0	0
Experiment III								
Quartz inhalation for 4 months, then BCG inhalation with quartz inhalation continued	24	0	2	11	3	0	8	19
Controls: BCG inhalation	17	13	0	0	4	0	0	0

TABLE 7

BCG Vaccination (Infection) in Experimental Tuberculosilicosis in Guinea Pigs

Summary of Data on Gross Pulmonary Tuberculous Disease

EXPERIMENTS	NUMBER OF PIGS	NUMBER OF PIGS SACRIFICED AT INTERVALS			NUMBER OF DEATHS			TOTAL WITH SPREADING DISEASE
		Negative	With non-spreading disease	With spreading disease	Negative	With non-spreading disease	With spreading disease	
Experiment IV								
BCG vaccination (intracutaneous); followed in two months by R_1 inhalation infection and quartz inhalaion	25	0	4	9	0	1	11	20
Controls: BCG vaccination followed in two months by R_1 inhalation infection	25	19	2	0	4	0	0	0
Quartz inhalation and R_1 inhalation infection	25	0	0	10	0	5	10	20
R_1 inhalation infection	25	4	18	0	2	1	0	0

in 8 animals. This increased number is in contrast to the fewer examples of progressive disease in Experiments I and II, and it indicates clearly the adverse influence of an established silicotic process upon the tissue resistance to tubercu-

losis. Progressive disease did not occur in the BCG nonsilicotic control animals; in fact, none of that group showed evidence of pulmonary infection (figures 12 and 15). The silicotic control animals with their uniformly distributed and isolated pulmonary lesions remained in marked contrast to the BCG-infected group, in which the lesions were confluent.

Positive cultures were obtained from 5 of 6 animals in the group exposed to quartz dust and then infected, but no growths resulted from 2 animals in the control group studied at the end of fourteen months (table 8). Here again, to

TABLE 8

Summary of Data on Cultures of Tissues from Infected Guinea Pigs

EXPERIMENTS	NUMBER OF ANIMALS CULTURED	NUMBER OF ANIMALS WITH NEGATIVE CULTURES	NUMBER OF ANIMALS WITH POSITIVE CULTURES	POSITIVE CULTURES FROM LUNGS AND TRACHEO-BRONCHIAL LYMPH NODES	POSITIVE CULTURES FROM LUNG ONLY	POSITIVE CULTURES FROM TRACHEO-BRONCHIAL LYMPH NODES ONLY	LONGEST TIME AFTER INFECTION POSITIVE CULTURES OBTAINED
Experiment I							
Intracutaneous BCG and quartz inhalation simultaneously	12*	9	3	2	0	1	18 months
Controls: Intracutaneous BCG	5*	2	3	1	1	2	18 months
Experiment II							
BCG inhalation and quartz inhalation simultaneously	7*	3	4	1	1	3	18 months
Controls: BCG inhalation	4*	4	0	—	—	—	—
Experiment III							
Quartz inhalation for 4 months, then BCG inhalation with quartz inhalation continued	6*	1	5	2	3	3	14 months
Controls: BCG inhalation	2*	2	0	0	0	0	—

* Individual guinea pig and time of culture indicated in tables 1 to 5.

date, enhanced virulence of the organisms has not been demonstrated by subinoculation of 10 mg. into guinea pigs.

Experiment IV: This experiment was planned to determine the efficacy of BCG vaccination in preventing tuberculosilicosis. Twenty-five healthy adult guinea pigs were vaccinated intracutaneously with 0.1 ml. of a BCG suspension prepared as in Experiment I. After two months all animals showed a positive tuberculin reaction. They then received a challenge infection by inhalation of the attenuated strain R_1 of the human tubercle bacillus (12) and were exposed eight hours daily to atmospheric quartz dust of high concentration as previously described. Three control groups, each consisting of 25 guinea pigs, were also introduced into the experiment. The animals in the first group were vaccinated

with BCG and infected with the R_1 strain, as described above; but they were not exposed to dust. The animals in the second group were not vaccinated; they were infected with R_1 tubercle bacilli and then placed in the dust room. The animals

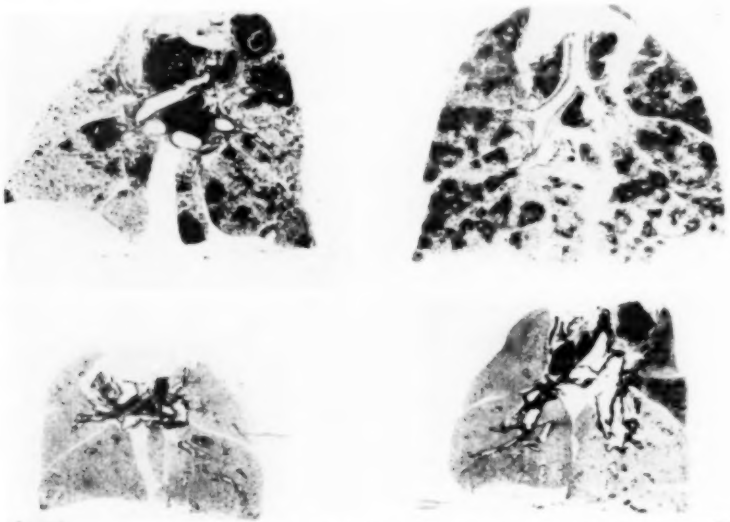

FIG. 17. (Upper left) Experiment IV. Guinea Pig Number 182. Intracutaneous BCG vaccination, two months, followed by R_1 inhalation and quartz inhalation. Killed at ten months. Note the areas of coalescent tuberculosilicosis. (1.5×)

FIG. 18. (Upper right) Experiment IV. Guinea Pig Number 231. R_1 and quartz inhalation control. Killed at ten months. Note the coalescent areas of tuberculosilicosis. The difference in extent of lesions in this animal and that shown in figure 17 is not considered significant. (1.5×)

FIG. 19. (Lower left) Experiment IV. Guinea Pig Number 224. Intracutaneous BCG vaccination, two months, followed by R_1 inhalation. Killed at ten months. The lungs are essentially normal; the occasional minute isolated subpleural tubercles do not show on this section. (1.5×)

FIG. 20. (Lower right) Experiment IV. Guinea Pig Number 272. R_1 inhalation only. Killed at ten months. The lungs are essentially normal except for incidental pyogenic pneumonia in the right cephalic lobes. The occasional minute isolated subpleural tubercles do not show on this section. (1.5×)

in the third group were not vaccinated but were infected with the R_1 strain and not exposed to dust.

The detailed results of these experiments are given in tables 4 and 7. None of the silicotic animals escaped tuberculous disease, indicating that no protection was given by the BCG vaccination against tuberculosilicosis (figure 17). The R_1-infected control animals exposed to quartz dust developed marked tuberculosilicosis as was expected (figure 18). In view of the findings in Experiments I, II, and III with BCG infection in the presence of quartz, the failure of BCG vaccina-

tion to prevent the development of tuberculosilicosis would have been anticipated.

In the control groups, BCG vaccination apparently inhibited the development of R_1 infection in guinea pigs. Only 2 of 25 animals revealed recognizable but nonspreading disease, the remainder being free of recognizable disease. In the R_1-infected controls, 19 of 25 showed recognizable but nonspreading disease.

DISCUSSION

This investigation demonstrates conclusively that the BCG strain organisms used in this study can produce progressive and fatal pulmonary tuberculosis in guinea pigs whose tissue resistance has been modified by the inhalation of quartz dust. Further, it shows that the BCG organisms isolated from the diseased tissues are still incapable of causing progressive disease when inoculated subcutaneously in a 10 mg. dose into healthy guinea pigs. These findings are not in accord with a published statement, made in another paper (13), which refers to a previous experiment conducted in this laboratory in 1931. A complete report of the 1931 experiment has never been published. Review of the protocol of that experiment discloses that various attenuated human and bovine organisms, including a BCG strain, were employed. The method used was similar to that for Experiment II of the present report, the animals being infected by inhalation of the BCG organisms and immediately placed in the dust room in which quartz dust was suspended in the atmosphere. There were important differences, however, between the two experiments. In the old experiment only 4 animals were used; the infecting dose was one-tenth of that employed in the present investigation; and the animals were sacrificed within 340 days, which, in the light of our current experiment, is too short a period for the development of the spreading tuberculosis.

What is the pathogenesis of the tuberculosis produced by the BCG organism in guinea pigs exposed to quartz? The same question may be asked concerning the progressive tuberculosis caused by the attenuated R_1 strain of human tubercle bacillus in silicotic guinea pigs. At present our knowledge is too meager to permit satisfying speculation as to the exact mechanism involved. It seems desirable, however, to consider some of the theories which have been advanced in this connection.

As yet there is no evidence to prove that the pathogenic properties of virulent tubercle bacilli depend on a toxin or on some particular constituent of the bacterial cell present in the virulent form and absent or reduced in avirulent forms. The main biologic difference between pathogenic and nonpathogenic tubercle bacilli appears to be their relative capacity to multiply in the host. Various theories have been presented to explain the proliferation or simulated virulence of tubercle bacilli in silicosis. Price (14) has stated that tubercle bacilli grow more rapidly upon egg medium to which small amounts of colloidal silicic acid have been added than in the egg medium without the colloidal silicic acid. Kettle (15) has championed the theory that the necrosis produced by localized accumulation of quartz particles in the tissue furnishes a favorable medium for the growth of tubercle bacilli. It has been observed that tubercle bacilli are numerous in a fresh

focus of silicotic necrosis (16). There is additional experimental evidence to support the view that silica enhances the growth of the tubercle bacillus. A pertinent study in this regard discloses that tubercle bacilli are much more numerous in lesions produced by quartz reactions than in those produced by various other dusts, such as granite, feldspar, chert, hematite, and gypsum (17). A possible explanation for the enhancement of the multiplication of tubercle bacilli by quartz is that quartz particles alter the phagocytic cells, thereby satisfying the metabolic requirements of the tubercle bacillus and favoring the progression of the tuberculous disease (18). Apparently, there are other factors which may alter the benign infection produced with BCG, for Dubos (19) has reported "that one of the BCG strains commonly used for immunization can cause severe pulmonary disease (and sometimes death) when injected in sufficient amounts into mice maintained on deficient diets."

In the light of the findings in this investigation, the statement of the adherents of BCG vaccination that the BCG organism is a stable strain or *virus fixe* must be reconsidered. This term, as used in the literature, appears to imply that the organisms are looked upon as being unable to produce progressive tuberculosis under any conditions. Birkhaug (20) has asserted that the chance of a spontaneous enhancement of virulence of BCG is still thought of as a possibility by competent and unbiased scientists.

One of the most important findings in this study has been the isolation of viable BCG organisms from the lungs and tracheobronchial lymph nodes of tuberculosilicotic animals and control animals at periods up to eighteen months after the organisms were injected intracutaneously. Therefore, it is apparent that BCG organisms may remain viable for at least eighteen months in the tissues of the guinea pig. Upon the evidence that such organisms may cause progressive tuberculosis in silicotic animals, BCG vaccination would appear to be contraindicated in persons who at some time might experience an increased susceptibility to tuberculosis by reason of factors such as exposure to quartz dust. We urge extreme caution, however, in any attempt to interpret these experimental results in terms of human experience. If these observations be valid, it is important to know the length of time during which the BCG organism remains viable in a host which is inhaling or has inhaled quartz dust, as well as in a host not subject to dust exposure. To answer this question, a series of experiments has been started to determine the duration of the viability of the BCG organisms in animal tissue subjected to various conditions of exposure to quartz dust. Further, it remains to be determined whether adverse influences other than those of quartz, or of deficient diet as reported by Dubos, can produce similar untoward results. It remains to be determined also whether or not such influences can produce similar results with other strains of BCG or with other attenuated tubercle bacilli.

SUMMARY

The experimental study herein reported demonstrates the following points:

1. BCG organisms spread from an intracutaneous site of inoculation in guinea

pigs and may localize in the viscera, including the lung and tracheobronchial lymph nodes.

2. The resistance of the host can be lowered by the tissue reaction to quartz particles so that the BCG organisms in the dose used for vaccination or for infection by inhalation can produce progressive and fatal pulmonary disease.

3. BCG organisms recovered from tissue exhibiting progressive disease have not been altered by growth in silicotic tissue, for they show no enhancement of virulence when subinoculated subcutaneously in large doses (10 mg.) into healthy guinea pigs.

4. Vaccination with BCG organisms does not prevent or retard the development of tuberculosilicosis produced by an infection with the attentuated R_1 strain of the human-type tubercle bacillus in the presence of inhaled quartz dust.

SUMARIO

La Vacunación BCG en la Silicosis

Recapitulando, este estudio experimental demuestra que:

1. Los microbios BCG se propagan de un sitio intracutáneo de inoculación, pudiendo localizarse en las vísceras, incluso el pulmón y los ganglios linfáticos tráqueobronquiales;

2. Puede mermar la resistencia del huésped la reacción histológica a las partículas de cuarzo de modo que los microbios BCG en la dosis utilizada para vacunación o infección por inhalación pueden producir afección pulmonar evolutiva y letal;

3. Los microbios BCG obtenidos de los tejidos que manifiestan enfermedad evolutiva no han sido alterados por su desarrollo en tejido silicótico, pues no revelan aumento de virulencia al ser subinoculados subcutáneamente a grandes dosis (10 mg.) en cobayos sanos;

4. La vacunación con BCG no impide ni retarda la aparición de tuberculosilicosis producida por infección con la cepa R_1 atenuada del bacilo tuberculoso de tipo humano, en presencia de polvo de cuarzo inhalado.

REFERENCES

(1) Holm, J.: BCG vaccination in Denmark, Pub. Health Rep., 1946, *61*, 1928.

(2) Aronson, J. D., and Palmer, C. E.: Experience with BCG vaccine in the control of tuberculosis among North American Indians, Pub. Health Rep., 1946, *61*, 802.

(3) Aronson, J. D.: Protective vaccination against tuberculosis with special reference to BCG vaccination, Am. Rev. Tubere., 1948, *58*, 258.

(4) Birkhaug, K.: BCG vaccination in Scandinavia, Am. Rev. Tubere., 1947, *55*, 234.

(5) Gardner, L. U.: Studies in experimental pneumoconiosis: Reactivation of healing primary tubercles in lung by inhalation of quartz, granite and carborundum, Am. Rev. Tubere., 1929, *20*, 833.

(6) Gardner, L. U.: Experimental tuberculosis as modified by dust inhalation, Nat. Tubere. A. Tr., 1929, *25*, 210.

(7) Policard, A., and Dufort, A.: Reserches experimentales sur les pneumoconiotuberculoses, Ann. med., 1937, *41*, 183.

(8) Gardner, L. U.: Etiology of pneumoconiosis, J.A.M.A., 1938, *111*, 1925.

(9) GARDNER, L. U.: The pathology and roentgenographic manifestations of pneumoconiosis, J.A.M.A., 1940, *114*, 535.
(10) BALDWIN, E. R., AND GARDNER, L. U.: Reinfection in tuberculosis, Am. Rev. Tubere., 1921, *5*, 429.
(11) GARDNER, L. U.: Studies in experimental pneumoconiosis: Inhalation of quartz dust, J. Indust. Hyg. & Toxicol., 1932, *14*, 18.
(12) GARDNER, L. U.: The history of the R_1 strain of tubercle bacillus, Am. Rev. Tubere., 1932, *25*, 5.
(13) STEENKEN, W., AND GARDNER, L. U.: R_1 strain of tubercle bacillus, Am. Rev. Tubere., 1946, *54*, 51.
(14) PRICE, R. M.: The influence of silica upon the growth of the tubercle bacillus, Canad. J. Research, 1932, *7*, 617.
(15) KETTLE, E. H.: The demonstration by fixation abscess of the influence of silica in determining *B. tuberculosis* infection, Brit. J. Exper. Path., 1924, *5*, 158.
(16) GARDNER, L. U.: Silicosis and related conditions, J. Indust. Hyg. & Toxicol., 1937, *19*, 111.
(17) VORWALD, A. J., AND LANDAU, A.: Influence of dust on tuberculous infection, Arch. Path., 1937, *24*, 8.
(18) VORWALD, A. J., AND DELAHANT, A. B.: The influence of silica on the natural and acquired resistance to the tubercle bacillus, Am. Rev. Tubere., 1938, *38*, 347.
(19) DUBOS, R. J.: Immunological aspects of BCG vaccination, Am. Rev. Tubere., 1949, *60*, 670.
(20) BIRKHAUG, K.: Virulence and tuberculogenic studies of sixty consecutive lots of BCG vaccine produced by standard technique, Am. Rev. Tubere., 1949, *59*, 567.

ANTIBACTERIAL SUBSTANCES IN SEED PLANTS ACTIVE AGAINST TUBERCLE BACILLI[1, 2, 3]

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(Received for publication May 1, 1950)

INTRODUCTION

In a previous study (1) of 161 species of seed plants, the extracts of 27 were found to have antibacterial activity against *Mycobacterium tuberculosis*. It is the purpose of this communication to describe briefly the methods of isolation and purification and some biological characteristics of two antibacterial substances obtained from 2 of these plant extracts. *Aloe vera* Linn. (*A. chinensis*, Baker) was chosen for further study because of its high activity *in vitro*, and *Menispermum canadense* Linn. because the crude extract was not inactivated when blood was incorporated into the assay medium. The extract of the latter plant was the only one of the 27 extracts mentioned previously which was not inactivated to some degree by whole blood. It is interesting to note that in folklore *M. canadense* was considered of value in the treatment of scrofula (2).

Although many of the antibacterial compounds isolated from higher plants may be found to be toxic or devoid of activity when administered to animals, this immense source of material should not be overlooked in a search for substances active against the acid-fast group of organisms. The current use of such substances as chaulmoogra oil (3, 4, 5) and *p*-aminosalicylic acid (6), a derivative of salicylic acid which occurs in plants, for the treatment of diseases caused by *Mycobacteria* makes it probable that other antibacterial substances from plant sources exist. Lupulon and humulon, two antibacterial substances derived from the hop plant, have recently been described (7), and may prove to be of value for the treatment of tuberculosis, although clinical studies have not yet been reported.

Methods and Materials

Method of assay: A 14- to 21-day culture of *M. tuberculosis* (H37) was used for all assays. To serial twofold dilutions in saline of the fraction being assayed was added melted and cooled glycerol beef extract agar, pH 7.0, or glycerol beef extract agar containing 10 per cent by volume of sheep blood. The medium was allowed to harden in a slanting position, inoculated with the test organism, and the cultures were incubated at 37°C. for six weeks. The highest dilution showing complete inhibition of growth was taken as the titer of the extract. In order to expedite the fractionation procedures, preliminary tests were made with the liquid medium described by Youmans (8). Serial dilutions were prepared in this medium and inoculated with a suspension of tubercle bacilli. If precipitates formed

[1] From the Michigan Department of Health, Lansing, and the Michigan Agricultural Experiment Station, East Lansing.

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[3] Journal Article No. 1141 from the Michigan Agricultural Experiment Station.

upon addition of the plant extract to the medium, they were removed by centrifugation before addition of the inoculum. Cultures were read after seven and fourteen days of incubation at 37°C. When a difference in titer between the liquid and solid cultures occurred, the titer obtained on the glycerol beef extract agar was used.

All of the extracts were sterilized by heating at 121°C. for fifteen minutes before being assayed since the active principles from both *A. vera* and *M. canadense* were heat stable.

Isolation and purification of barbaloin: Whole dried Curacao Aloe (USP Penick) was powdered, mixed with Hy-Flo Super-Cel (Johns-Manville) and extracted with ethyl acetate in a Soxhlet extractor. The extract, when freed of solvent, gave a crude mixture of aloins, about 30 per cent by weight of the dried aloe. The crude aloins were recrystallized from a mixture of one volume of methanol and two volumes of chloroform. The resulting crystalline product contained a mixture of the isomers, barbaloin and isobarbaloin. Barbaloin was separated from its isomer by the method of Leger (9). It has a melting point of 145° to 147°C. and $[\alpha]_D^{25} = +22.5°$ (1 per cent aqueous solution). The penta-acetyl derivative was prepared by acylating with acetic anhydride and sodium acetate. It melted at 100° to 103°C. These constants agree with those given in the literature for barbaloin (10).

Isolation and purification of the active principle of M. canadense: The active principle was isolated from the roots of *M. canadense*. The method of obtaining it was essentially the same as that employed by Manske (11) for the isolation of dauricine. The substance isolated responds to a number of tests and has chemical and physical properties similar to dauricine. The constants obtained did not agree with those reported by Manske (11). A chloroform solution of the substance, when adsorbed chromatographically on a column packed with 2 $CaSO_4$-H_2O, yielded several alkaloids having different melting points. The most abundant alkaloid having antibacterial activity was characterized by preparing the dimethiodide. This was recrystallized from methanol until a constant melting point and rotation were attained.

The following properties were observed:

Melting point—188° (decomp.)

Rotation—$[\alpha]^{26} = -139°$ in methanol where C = 0.35 per cent

Solubility—Soluble in hot methanol, hot ethanol, slightly soluble in water; and insoluble in chloroform, acetone, and dioxane.

Analysis—$C_{40}H_{50}O_8N_2I_2$

Calculated.	C 51.1	H 5.4	N 3.0	OCH_3 13.2	I 27.0
Found.	C 51.0	H 5.5	N 3.1	OCH_3 13.2	I 27.0

RESULTS

Biological properties of barbaloin: The activity *in vitro* against various organisms is given in table 1. It may be seen that *M. tuberculosis* and *Bacillus subtilis* are more sensitive to this substance than any of the other organisms tested. Higher concentrations than 5 mg. per ml. could not be tested because of the insolubility of the compound.

Barbaloin is approximately half as active when blood is incorporated into the test medium. Using *M. tuberculosis*, strain H37Rv, as a test organism, the inhibitory concentration of barbaloin diluted in glycerol beef extract agar was found to be 0.125 mg. per ml., while 0.25 mg. per ml. was required to inhibit this organism when 10 per cent of sheep blood was incorporated into the medium.

All concentrations of barbaloin tested were not bactericidal for the tubercle

bacillus even after seven days of exposure to the substance. Barbaloin was prepared in concentrations of 2.0, 1.0, 0.5, 0.25, and 0.125 mg. per ml. in Youmans medium and inoculated with a suspension of tubercle bacilli prepared from a culture of H37 grown on Petragnani's medium. After seven days of incubation at 37°C., growth was observed only in the tube containing 0.125 mg. per ml. of barbaloin. The tubes were centrifuged and the sediment washed twice with

TABLE 1

Activity of Barbaloin on Various Organisms

MICROORGANISM	CULTURE NUMBER OR SOURCE	CONCENTRATION REQUIRED FOR INHIBITION OF GROWTH (MG. PER ML.)*
Aerobacter aerogenes	618	>5.0
Bacillus subtilis	231	0.125
Corynebacterium diphtheriae	P. W S	1.0
Diplococcus pneumoniae, Type III	N.I.H.	2.5
Escherichia coli	621	>5.0
Klebsiella pneumoniae	N.I.H.	>5.0
Mycobacterium phlei	1201	>2.0
Mycobacterium smegmatis	1212	>2.0
Mycobacterium tuberculosis	H37Rv	0.25
Mycobacterium	607	>2.0
Proteus vulgaris	1414	>5.0
Pseudomonas aeruginosa	R-P-CC	>5.0
Salmonella typhosa	710	>5.0
Shigella dysenteriae, Flexner type	5001	>5.0
Staphylococcus aureus	209P	2.5
Streptococcus pyogenes	286	>5.0
Aspergillus flavus	1035	>2.0
Aspergillus niger	7416	>2.0
Histoplasma capsulatum	Duke University	>2.0
Penicillium notatum	832	>2.0
Trichophyton mentagrophites	M.D.H.	>2.0

* Broth prepared according to the FDA (Federal Register, 1945) was employed in the majority of these tests, with the addition of agar for the tests with fungi. Exceptions were as follows: *D. pneumoniae* and *Str. pyogenes* (Felton's medium); *C. diphtheriae* (veal infusion broth); *Mycobacteria* (glycerol beef extract agar).

saline and inoculated into tubes of Petragnani's medium. After incubation for six weeks, growth was observed in all tubes of the subcultures.

When injected intraperitoneally, the maximum dose tolerated by 20-gram Swiss mice was 200 mg. per kg. of body weight.

Biological properties of an alkaloid preparation from M. canadense: The activity of an alkaloid complex from *M. canadense* against various organisms is given in table 2. The organisms most sensitive to this substance were *M. tuberculosis*, *D. pneumoniae*, *B. subtilis*, and *M. phlei*.

Blood did not inhibit the action of this alkaloid complex. When grown on gly-

cerol-beef extract agar the activity was found to be 0.125 mg. per ml., and the same activity was obtained when 10 per cent of whole sheep blood was added to it.

TABLE 2

Activity of an Antibacterial Alkaloid Preparation from Menispermum Canadense on Various Organisms

MICROORGANISM*	CULTURE NUMBER OR SOURCE	CONCENTRATION REQUIRED FOR INHIBITION OF GROWTH (MG. PER ML.)*
Aerobacter aerogenes	618	5.0
Bacillus subtilis	231	0.31
Diplococcus pneumoniae Type III	N.I.H.	0.15
Escherichia coli	621	1.25
Klebsiella pneumoniae	N.I.H.	2.5
Mycobacterium phlei	1201	0.5
Mycobacterium smegmatis	1212	1.0
Mycobacterium tuberculosis	H37	0.13
Proteus vulgaris	1414	>5.0
Pseudomonas aeruginosa	R-P-CC	5.0
Salmonella typhimurium	9	2.5
Shigella dysenteriae, Flexner type	5001	1.25
Staphylococcus aureus	209P	2.5
Streptococcus pyogenes	286	2.5
Aspergillus flavus	1035	>2.0
Aspergillus niger	7416	>2.0
Histoplasma capsulatum	Duke University	>2.0
Penicillium notatum	832	>2.0
Streptomyces griseus	4	1.0
Trichophyton mentagrophytes	M.D.H.	>2.0

* For type of medium see table 1.

TABLE 3

Growth of Subcultures Inoculated with Tubercle Bacilli Which Had Been Incubated in Horse Serum Containing the Alkaloid Complex from Menispermum

DAYS OF INCUBATION IN SERUM	CONCENTRATION OF THE ALKALOID COMPLEX (MG. PER ML.)						
	2.0	1.0	0.5	0.25	0.125	0.0625	Control
1	−	+	+	+	+	+	+
2	−	−	+	+	+	+	+
3	−	−	−	+	+	+	+
6	−	−	−	−	+	+	+
14	−	−	−	−	−	+	+

The complex was more active at pH 7.0 than at pH 5.5. At a pH of 7.0 a titer of 0.125 mg. per ml. was obtained while at a pH of 5.5 the complex did not inhibit tubercle bacilli in concentrations up to 2.0 mg. per ml. Assays were not performed at a pH higher than 7.0 because the complex becomes water insoluble at a pH greater than 7.2.

The material was found to be bactericidal even in the presence of blood serum. Serial dilutions of the complex were made in normal horse serum and inoculated with a heavy suspension of *M. tuberculosis*, strain H37. At the intervals shown in table 3, 0.1 ml. of the seeded dilutions was removed from each tube and added to 5.0 ml. of Youmans liquid medium. The results, given in table 3, show that the alkaloid complex was bactericidal in concentrations as low as 0.125 mg. per ml.

When injected intraperitoneally into 20-gram Swiss mice the maximum tolerated dose was 100 mg. per kg. of body weight.

At present, the toxicity of barbaloin and the alkaloid complex from *M. canadense* precludes their clinical use. Recent studies of the dimethiodide derivative of an alkaloid of this complex, however, have shown that toxicity and antibacterial activity may be independent of each other. It is possible, therefore, that a less toxic antibacterial substance can be prepared from this complex. Studies on this phase are in progress.

SUMMARY

An antibacterial principle present in *Aloe vera* which inhibits growth of tubercle bacilli has been found to be the glycoside barbaloin. The antibacterial activity of extracts from *Menispermum canadense* is due to a mixture of alkaloids. The methods of isolation and some of the biological properties of these antibacterial substances are described.

SUMARIO

Sustancias Antibacterianas Activas contra el Bacilo Tuberculoso en las Plantas de Semilla

Un principio antibacteriano presente en el *Aloe vera*, que inhibe la proliferación de los bacilos tuberculosos ha resultado ser el glucósido barbaloína. La actividad antibacteriana de los extractos del *Menispermum canadense* procede de una mezcla de alcaloides. El trabajo actual describe las técnicas de aislamiento y algunas de las propiedades biológicas de dichas sustancias antibacterianas.

REFERENCES

(1) Gottshall, R. Y., Lucas, E. H., Lickfeldt, A., and Roberts, J. M.: The occurrence of antibacterial substances active against *Mycobacterium tuberculosis* in seed plants. J. Clin. Investigation, 1949, *28*, 920.

(2) Grieve, M., and Leyel, H.: A Modern Herbal. Harcourt, Brace & Company, New York, 1931.

(3) Culpepper, W. L., and Ableson, M.: Chaulmoogra oil in the treatment of tuberculosis. J. Lab. & Clin. Med., 1921, *6*, 415.

(4) Walker, E. L., and Sweeney, M. A.: The chemotherapeutics of the chaulmoogra acid series and other fatty acids in leprosy and tuberculosis. J. Infect. Dis., 1920, *26*, 238.

(5) Lissner, H. H.: Chaulmoogra oil esters in the treatment of pulmonary tuberculosis. Am. Rev. Tubere., 1923, *7*, 257.

(6) Lehmann, J.: Para-aminosalicylic acid in the treatment of tuberculosis: Preliminary communication. Lancet, 1946, *1*, 15.

(7) LEWIS, J. C., ALDERTON, G., CARSON, J. F., REYNOLDS, D. M., AND MACLAY, W. D.: Lupulon and humulon—antibiotic constituents of hops, J. Clin. Investigation 1949, *28*, 916.

(8) YOUMANS, G. P.: Subsurface growth of virulent human tubercle bacilli in a synthetic medium, Proc. Soc. Exper. Biol. & Med., 1945, *57*, 122.

(9) LEGER, E.: The aloins, Ann. de chim., 1916, *6*, 318.

(10) JOWETT, H. A. D., AND POTTER, C. E.: The constitution of barbaloin, J. Chem. Soc. London, 1905, *87*, 878.

(11) MANSKE, R. H. F.: An alkaloid from *Menispermum canadense L.*, Canad. J. Research, 1943, *21B*, 13.

ISOLATION OF TUBERCLE BACILLI FROM FECES AND GASTRIC CONTENTS OF INTRAVENOUSLY INFECTED MICE[1,2]

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INTRODUCTION

Studies concerning the experimental chemotherapy of tuberculosis frequently are performed on mice infected intravenously with strains of *Mycobacterium tuberculosis* of either the human or bovine variety (1–7). In the course of such studies employing mice of the Strong A strain infected with various amounts of the human (H37Rv) or bovine (Ravenel) variety of *M. tuberculosis*, we became interested in the possibility of excretion of virulent tubercle bacilli by these animals. Such knowledge seemed desirable to determine the risk of exposure of laboratory workers to infection from this source.

EXPERIMENTS

Twenty mice were infected intravenously with 0.05 mg. of the human strain H37Rv of *M. tuberculosis*. Another 50 mice were infected by the same route with various amounts of the bovine Ravenel strain of *M. tuberculosis* ranging from 0.05 to 0.4 mg. The animals then were distributed in groups of 5 into cages with solid metal floors covered with wood shavings.

Collection of feces from these animals was begun seven days after infection and was repeated three or four times during the course of the disease. On the day preceding collection of feces, the mice were transferred to previously sterilized cages to assure collection of fresh fecal material.

Specimens consisting of five pieces of fecal matter were collected from each of the cages and were transferred to sterile mortars and ground in sterile phosphate buffer solution. The individual suspensions were then mixed with equal volumes of 2 per cent oxalic acid and incubated at 37° C. for thirty minutes. After washing by centrifugation with phosphate buffer solution, each of the sediments was inoculated onto two slants of Herrold's egg-yolk medium containing 0.02 per cent of malachite green.

Growth characteristic of *M. tuberculosis* was observed in only three tubes representing specimens collected from mice previously infected with 0.4 mg. and 0.2 mg. of the Ravenel strain and 0.05 mg. of the H37Rv strain. The respective specimens had been collected fourteen, twenty-one, and twenty-six days following infection. The growth in these tubes consisted of acid-fast rods. The virulence of the three isolates was determined by injecting guinea pigs with approximately 0.1 mg. of the respective growth. The animals died from twenty-seven to fifty-

[1] From the Department of Bacteriology, Northwestern University Medical School, Chicago 11, Illinois.

[2] This investigation was supported (in part) by a research grant from the National Institutes of Health, Public Health Service.

nine days following infection and showed typical tuberculous lesions on autopsy. Tubes in which no visible growth indicative of *M. tuberculosis* had occurred after an incubation period of ninety days were discarded.

Investigating the possible source of the bacteria in the feces, it was noticed that macroscopically discernible lesions were absent in the intestinal tract of these mice. It was therefore thought possible that the bacteria might have been introduced into the gastrointestinal tract with swallowed material originating from the extensive pulmonary lesions.

In order to test this assumption, gastric lavages were carried out on infected mice immediately after their death from the disease. The stomach was clamped off above the cardia and below the pylorus. A small volume of sterile phosphate buffer solution was then introduced into the stomach by puncture through the stomach wall by means of a 27-gauge needle attached to a tuberculin syringe. The aspirated stomach contents of 5 mice were pooled and concentrated by the oxalic acid method. The sediment was then cultured as described above, except that three tubes of culture medium were employed for the gastric washings from each group of 5 mice.

The stomach washings of a total of 15 mice were cultured in this manner. Growth typical of *M. tuberculosis* appeared after an incubation period of twenty-one days in two of the three culture tubes made from the gastric washings of one of the three groups of mice. The pathogenicity of one of these cultures was ascertained by injecting a suspension of the organism into a guinea pig. This animal was sacrificed twenty-two days following infection and on autopsy showed lesions typical of tuberculosis in guinea pigs.

DISCUSSION

That mice, following intravenous injection of virulent tubercle bacilli, may excrete such organisms in their feces should be of concern as a possible source of laboratory infections. In view of the results of the experiments reported above in which only small quantities of feces were used for culturing, it would seem possible that in reality greater numbers of bacilli might be excreted by the infected animals than our findings would indicate.

The positive results obtained with the gastric washings of these animals seem to support our assumption concerning the source of the organisms in the feces. It is possible, however, that organisms might enter the intestinal tract by biliary excretion or from microscopic lesions in the intestinal mucosa. In view of the observation of Raleigh and Youmans (2) on the occurrence of microscopic renal lesions in mice infected with *M. tuberculosis*, it also seems possible that feces might become contaminated with bacteria from the urine of these animals.

SUMMARY

Isolation of virulent tubercle bacilli of both the human and the bovine varieties from the feces of experimentally infected mice has been accomplished. Moreover, virulent tubercle bacilli also have been found in the gastric contents

of such mice. These findings suggest that mouse feces may be a possible source of tuberculous infection for laboratory personnel.

SUMARIO

Aislamiento de los Bacilos Tuberculosos de las Heces y Contenido Gástrico de los Ratones Infectados Endovenosamente

En este estudio se llevó a cabo el aislamiento de bacilos tuberculosos virulentos de las variedades tanto humana cuanto bovina en las heces de ratones infectados experimentalmente. Además, descubriéronse bacilos tuberculosos virulentos en el contenido gástrico de dichos ratones.

Estos hallazgos indican que las heces murinas pueden constituir una posible causa de infección tuberculosa para el personal de laboratorio.

REFERENCES

(1) Youmans, G. P., and McCarter, J. C.: Streptomycin in experimental tuberculosis: Its effect on tuberculous infections in mice produced by *M. tuberculosis* var. *hominis*, Am. Rev. Tuberc., 1945, *52*, 432.

(2) Raleigh, G. W., and Youmans, G. P.: The use of mice in experimental chemotherapy of tuberculosis, J. Infect. Dis., 1948, *82*, 197.

(3) McKee, C. M., Rake, G., Donovick, R., and Jambor, W. P.: The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: I. Choice and standardization of culture, Am. Rev. Tuberc., 1949, *60*, 90.

(4) Donovick, R., McKee, C. M., Jambor, W. P., and Rake, G.: The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: II. Choice of mouse strain, Am. Rev. Tuberc., 1949, *60*, 109.

(5) Rake, G., Jambor, W. P., McKee, C. M., Pansy, F., Wiselogle, F. Y., and Donovick, R.: The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: III. The standardized test, Am. Rev Tuberc., 1949, *60*, 121.

(6) Donovick, R.: The use of the mouse in experimental tuberculosis, Ann. New York Acad. Sc., 1949, *52*, Art. 5, 671.

(7) Baker, M. J., Schlosser, M. E., and White, H. J.: A method for evaluating antitubercular activity in mice, Ann. New York Acad. Sc., 1949, *52*, Art. 5, 678.

COMPARISON OF TWO SOLID MEDIA FOR TESTING SENSITIVITY TO STREPTOMYCIN[1]

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INTRODUCTION

The increasing use of streptomycin in the treatment of tuberculosis and the importance of determining the sensitivity of strains of tubercle bacilli to this drug raise a question as to the best medium for use in testing sensitivity to streptomycin. A medium which (a) promotes early growth, (b) is not subjected to heat after the addition of streptomycin, (c) permits the direct inoculation of pathologic specimens, and (d) supports luxuriant growth from small inocula would be of great advantage.

Although both liquid (1, 2) and solid media (3) have been advocated for determining the sensitivity of tubercle bacilli to streptomycin, solid media are preferred because they permit the direct inoculation of pathologic material and also give some indication of the relative number of resistant and sensitive organisms. Direct inoculation has the advantage of eliminating the necessity for subculturing, thereby saving considerable time in reporting results of tests.

Previously, various methods for preparing the inoculum of pure culture have been advocated for the testing of sensitivity of *Mycobacterium tuberculosis* to streptomycin. This laboratory has compared three of the most popular methods, using one hundred pure cultures, and found the method described in this paper the most satisfactory from the standpoint of ease and rapidity of preparation. The amount of inoculum, within the range of 0.1 to 3 mg. per ml., has almost no effect on the results of the assay. Within these limits, the more inoculum, the more rapid and extensive is the growth; hence the results can be reported faster.

Among the media evaluated by this laboratory have been various modifications of the Dubos and Davis basal medium (4) of the following compositions:

a) Base + 0.05 per cent Tween 80 + 0.5 per cent albumin
b) Base + 0.05 per cent oleic acid + 0.5 per cent albumin
c) Base + 10 per cent plasma
d) Base + 10 per cent citrated whole blood + 1.5 per cent agar in plates
e) Base + 0.05 per cent Tween 80 + 0.5 per cent albumin + 1.5 per cent agar in plates.

All of these were abandoned eventually because (*1*) the liquid media were easily contaminated and for that reason only pure cultures of tubercle bacilli could be assayed; (*2*) no characteristic growth was present in the liquid media since it varied from diffuse to granular or stringy growth; and (*3*) with liquid media, small differences in the amount of growth were not easily observed, nor

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was it possible to detect the presence of mixtures of resistant and sensitive organisms. The two solid modifications of the Dubos-Davis medium were discarded because of the difficulty in handling the plates, the rapid dehydration and, in the case of albumin-agar plates, the difficulty of examining the plates grossly since there was a poor contrast of colony and medium.

This report is based on a comparison of two other solid media employed by the Tuberculosis Evaluation Laboratory in the routine determination of sensitivity to streptomycin: the Jensen and Holm modification of Löwenstein's medium (5) and modified Herrold's egg-yolk-agar medium (3, 6, 7).

Materials and Methods

Herrold's egg-yolk-agar medium was prepared according to the following formula:

1. Bacto-Difco Nutrient—dehydrated agar ..... 23 gm.
   Containing: Bacto-beef extract ..... 3 gm.
   Bacto-peptone ..... 5 gm.
   Bacto-agar ..... 15 gm.
2. Distilled water ..... 750 ml.
3. Glycerol (reagent grade) ..... 10 ml.
4. Malachite green (2 per cent aqueous solution) ..... 10 ml.
   Autoclave for 20 minutes at 15 lbs. pressure (121°C.)
5. Dispense 150 ml. amounts in flasks; cool to 47°C. (This agar can be kept in the refrigerator and remelted before use.)
6. Add streptomycin in desired concentrations.
7. Eggs are scrubbed and rinsed in water and soaked in 70 per cent alcohol for 15 minutes: 50 ml. of sterile *fresh* egg yolk are added to each flask; mix well by rotating flask.
8. The streptomycin and egg yolk are added just before tubing, 5 ml. per test tube.
9. Incubate for 48 hours as a test for sterility.

Löwenstein-Jensen medium was prepared as outlined below.

1. Salt solution
   Monopotassium phosphate ..... 2.4 gm.
   Magnesium sulfate ..... 0.24 gm.
   Magnesium citrate ..... 0.6 gm.
   Asparagine ..... 3.6 gm.
   Glycerol (twice distilled) ..... 12 ml.
   Redistilled water ..... 600 ml.
2. The salt solution is heated in a flask until all ingredients are dissolved and then placed in a water bath at 56°C. for 2 hours. This solution may be kept in the refrigerator overnight if necessary. On the following day, 30 gm. of potato flour are added to the flask.
3. The flask is heated, with continual shaking, in a boiling water bath until the content is clear, and then heated for 15 additional minutes. Finally, the flask is left standing in a water bath at 56°C. for one hour.
4. Only fresh eggs are employed. The eggs are soaked in a 5 per cent soda and soap solution for 30 minutes, then placed in running cold water until this water is perfectly clear. They are broken into a sterile flask, shaken well, and filtered through sterile gauze.
5. One liter of eggs is mixed with the flask of salt solution and to this is added 20 ml.

of a 2 per cent aqueous solution of malachite green. The mixture is left standing at room temperature for one hour before tubing.

6. Dispense 200 ml. amounts in sterile flasks.
7. Add streptomycin in desired concentrations and tube 5 ml. per test tube. Fifty per cent more streptomycin was added in excess of that desired for the final concentration since it has been estimated by chemical assay that 50 per cent of the drug is lost during inspissation (8, 9).
8. Inspissate for 40 minutes at 85°C.
9. Incubate for 48 hours as a test for sterility.

For each test, three tubes containing streptomycin in concentrations of 100, 10, and 2 γ per ml. of medium, respectively, and two control tubes containing no streptomycin were employed.

Both pure cultures of tubercle bacilli and pathologic specimens were used in the study. Pure cultures were received from various laboratories of state health departments. The pathologic specimens, consisting of sputum, gastric washings, urine, pus, feces, spinal fluid, and tissues were received from Lawson Veterans Administration Hospital and U. S. Veterans Administration Hospital No. 48, Atlanta, Ga. Pure cultures were prepared for inoculation by homogenizing a spadeful of the culture against the side of a test tube containing sterile distilled water. The pathologic specimens were digested and concentrated according to a standard technique utilizing sodium hydroxide (10). In both procedures, 0.1 ml. of inoculum was placed on each tube of medium. After inoculation, the tubes were incubated at 37°C. in a slanted position until examined for the first time at the end of 2 weeks. They were examined at weekly intervals thereafter until discarded at the end of 5 weeks. A record was kept of the total number of colonies and time of their first appearance.

A total of 174 pathologic specimens and 356 pure cultures was tested on Löwenstein's medium and Herrold's egg-yolk-agar medium.

RESULTS

The results of assays performed with pure cultures are given in table 1.

It will be noted that 96.1 per cent of the assays on Löwenstein's medium were satisfactory, while 94.1 per cent on Herrold's medium were satisfactory. The majority of variations between tests of sensitivity (growth in a higher concentration of streptomycin on one medium) did not occur until the fifth week. Until the end of the fourth week there was agreement between the two media in all concentrations of streptomycin in which growth occurred. Only 6 cultures were positive on Herrold's medium and negative on Löwenstein's, while 12 were positive on Löwenstein's medium and negative on Herrold's.

The results of tests of sensitivity performed on pathologic specimens are given in table 2.

It will be noted that 97.1 per cent of the assays performed with pathologic specimens were satisfactory on Löwenstein's medium and 90.8 per cent were satisfactory on Herrold's medium. Again, the latter medium yielded more negative cultures as well as more instances in which major variations were noted.

Tables 3 and 4 show the distribution of reportable results at weekly intervals and are based on cultures reported as "satisfactory" in tables 1 and 2.

Reportable growth is considered here as that in which no change in the report

TABLE 1

Sensitivity to Streptomycin of 356 Pure Cultures of Tubercle Bacilli

Results of Assays Performed on Löwenstein's and Herrold's Media

	LÖWENSTEIN'S MEDIUM		HERROLD'S MEDIUM	
	Number	Per cent	Number	Per cent
Test satisfactory*	342	96.1	335	94.1
Test unsatisfactory (no growth)	6	1.7	12	3.4
Test unsatisfactory (contaminated)	2	0.5	3	0.8
Test unsatisfactory (major variations)†	6	1.7	6	1.7
Growth in a higher concentration of streptomycin	22	6.4	42	12.5

* Satisfactory growth was reported in all tests in which there were 50 or more colonies on the control tubes and on those tests that did not fall in the other unsatisfactory groups.

† Tests of sensitivity which had major variations were tests in which the end points on the two media differed by more than one dilution interval of streptomycin or in which, on either of the two media, no growth occurred in the lower concentrations of streptomycin while growth appeared in the higher concentrations.

TABLE 2

Sensitivity to Streptomycin of Tubercle Bacilli in 174 Pathologic Specimens

Results of Assays Performed on Löwenstein's and Herrold's Media

	LÖWENSTEIN'S MEDIUM		HERROLD'S MEDIUM	
	Number	Per cent	Number	Per cent
Test satisfactory*	169	97.1	158	90.8
Test unsatisfactory (no growth)	1	0.6	6	3.4
Test unsatisfactory (contaminated)	0	0.0	0	0.0
Test unsatisfactory (major variations)†	4	2.3	10	5.8
Growth in a higher concentration of streptomycin	6	3.6	18	11.4

* See Table 1.

† See Table 1.

TABLE 3

Tests of Streptomycin Sensitivity Yielding Reportable Results from Pure Cultures at Various Intervals

EARLIEST TIME AT WHICH RESULTS WERE REPORTABLE	LÖWENSTEIN'S MEDIUM		HERROLD'S MEDIUM	
	Number	Per cent	Number	Per cent
2 weeks	128	37.4	128	38.2
3 weeks	89	26.0	91	27.2
4 weeks	72	21.1	61	18.2
5 weeks	53	15.5	55	16.4

of results was necessary even after continued incubation for two, three, four, or five weeks. Although the colony count in those tubes showing growth may have increased at a later date, no new growth was initiated in higher concentrations of streptomycin which had previously shown no growth.

TABLE 4

Tests of Streptomycin Sensitivity Yielding Reportable Results from Pathologic Specimens at Various Intervals

EARLIEST TIME AT WHICH RESULTS WERE REPORTABLE	LÖWENSTEIN'S MEDIUM		HERROLD'S MEDIUM	
	Number	Per cent	Number	Per cent
2 weeks	43	25.4	43	27.2
3 weeks	69	40.8	49	31.0
4 weeks	30	17.8	44	27.9
5 weeks	27	16.0	22	13.9

From the data in tables 3 and 4 it may be seen that more than 50 per cent of all sensitivity tests could be reported at the end of 3 weeks.

DISCUSSION

As stated in the introduction, this laboratory has examined various liquid and solid media to evaluate their adaptability to routine testing of sensitivity of tubercle bacilli to streptomycin. Löwenstein's medium was used as a basis for comparison in testing all of these media, both as regards colony count and verification of viability of the organism in the test specimen. A more extensive comparison was made between Löwenstein's and Herrold's media.

It will be noted that certain advantages and disadvantages are inherent in each of the two media concerned in the present report. Herrold's egg-yolk agar has the advantage of being relatively easy to prepare since the basic ingredients are materials readily available in most general bacteriological laboratories. Moreover, no inspissation is required; hence allowance need not be made for any loss of streptomycin due to heat. It should be noted, however, that occasional tubes of Herrold's medium did not support growth nor did the medium prove to be quite as sensitive as evidenced by the slightly higher percentage of failures. The reason for this finding is not known, although it has been suggested that agar is somewhat inhibitory to the growth of the tubercle bacilli (11).

Attention is called to line five of tables 1 and 2. In table 1, this refers to 22 tests in which, on Löwenstein's medium, some growth occurred in tubes containing streptomycin while no growth occurred on Herrold's medium in tubes containing the same concentrations of streptomycin. In the same table, the results of 42 tests are noted in which growth occurred in certain concentrations of streptomycin on Herrold's medium while no growth occurred in the corresponding tubes of Löwenstein's medium. The growth in such tubes of either medium appeared at the end of four or five weeks and was so slight (one to ten colonies) as to be reported routinely, for clinical purposes, as "negative." All control tubes showed luxuriant growth at the end of two weeks.

Although the clinical interpretation of the delayed growth may be of the greatest importance to both patient and physician, no explanation of this delay is available at present. It is conceivable that a few cells might acquire resistance to streptomycin as a result of the four or five weeks' contact with the drug. It is also possible that the delayed growth could result from a very few resistant cells initially present in the culture. Repeated experiments here show that it is not due to significant diminution of the concentrations of streptomycin in the medium during the period of incubation.

It would seem that appearance of growth on one medium but not in corresponding tubes of the other medium, regardless of time of appearance, might well be due to a sampling error. That is to say, the culture might contain a very few cells capable of growth in the presence of, say, 10 γ per ml. of medium and, in pipetting, a few of these cells might be transferred to the Löwenstein's but not to the Herrold's medium, or vice versa. This laboratory has found that this sampling error can be largely eliminated by inoculating the tubes, in sequence, from the highest concentration of streptomycin to the control tubes rather than from the control tubes to the highest concentration of streptomycin. On conducting several assays of sensitivity using the same inoculum, it has been found that about one of ten assays will show this error.

In order not to deprive of treatment those patients from whom are recovered strains having low percentages of resistant cells, it is common practice to ignore colony counts below a certain arbitrary figure and to report as "negative" tests showing less than ten colonies. The propriety of such a routine in reporting results is debatable.

Disagreements after the fourth week suggest the possibility that results of tests of sensitivity might not be entirely reliable after prolonged incubation.

SUMMARY AND CONCLUSIONS

1. A total of 356 pure cultures of tubercle bacilli and 174 pathologic specimens have been tested for sensitivity to streptomycin on Herrold's egg-yolk-agar medium and on Löwenstein's medium.

2. Results of tests with the two media agreed in 94.5 per cent of the 530 comparisons made at the end of four weeks and 86.6 per cent at the end of five weeks.

3. On Löwenstein's medium from the same inoculum, the results are more consistent and less likely to be negative than on Herrold's medium. With pathologic specimens, growth occurs earlier and more profusely on Löwenstein's than on Herrold's medium.

4. Disagreements in results usually appeared in the fifth week of incubation. The significance of these discrepancies is difficult to interpret at present.

5. Löwenstein's medium is preferred in this laboratory because it gives more accurate and consistent results than Herrold's medium. For laboratories not equipped to prepare Löwenstein's medium, Herrold's medium may be recommended, however, because it is more readily available and because it yields results nearly as good as Löwenstein's medium.

SUMARIO Y CONCLUSIONES

Comparación de Dos Medios Sólidos para Determinar la Sensibilidad a la Estreptomicina

1. Un total de 356 cultivos puros de bacilos tuberculosos y de 174 ejemplares patológicos fué comprobado en cuanto a sensibilidad a la estreptomicina en el medio de agar-yema de huevo de Herrold y en el medio de Lowenstein.

2. Los resultados de las pruebas ejecutadas con los dos medios convinieron en 94.5 por ciento de las 530 comparaciones realizadas.

3. En el medio de Lowenstein, utilizando el mismo inóculo, los resultados son más constantes y menos susceptibles de ser negativos que en el de Herrold. Con los ejemplares patológicos, las colonias son más tempranas y más profusas en el medio de Lowenstein que en el de Herrold.

4. Los desacuerdos en los resultados aparecieron por lo general en la quinta semana de incubación. Es difícil interpretar por ahora el significado de esas discrepancias.

5. En el laboratorio de los AA., prefieren el medio de Lowenstein por dar resultados más exactos y constantes que el de Herrold. Sin embargo, para los laboratorios que no cuentan con los elementos necesarios para preparar el medio de Lowenstein puede recomendarse el medio de Herrold por ser más accesible y dar resultados casi tan buenos como el medio de Lowenstein.

REFERENCES

(1) Fisher, M. W.: Sensitivity of tubercle bacilli to streptomycin, an *in vitro* study of some factors affecting results in various test media, Am. Rev. Tuberc., 1948, *57*, 58.

(2) Wolinsky, E., and Steenken, W., Jr.: Effect of streptomycin on the tubercle bacillus: The use of Dubos and other media in tests for streptomycin sensitivity, Am. Rev. Tuberc., 1947, *55*, 281.

(3) Karlson, A. G., and Needham, G. M.: Determination of streptomycin sensitivity of tubercle bacilli by use of egg-yolk-agar medium, Proc. Staff Meet., Mayo Clin., 1948, *23*, 401.

(4) Dubos, R. J., and Middlebrook, G.: Media for tubercle bacilli, Am. Rev. Tuberc., 1947, *56*, 334.

(5) Holm, J., and Lester, V.: Diagnostic demonstration of tubercle bacilli, Acta tuberc. Scandinav., 1941, *16*, 3; Pub. Health Rep., 1947, *62*, 847.

(6) Herrold, R. D.: Egg-yolk-agar medium for the growth of tubercle bacilli, J. Infect. Dis., 1931, *48*, 236.

(7) From the Laboratory Subcommittee of the American Trudeau Society (to be published).

(8) Steenken, W. Jr.: Personal communication.

(9) Drummond, M. C.: Personal communication.

(10) Spendlove, G. A., Cummings, M. M., and Patnode, R. A.: Demonstration of tubercle bacilli in sputum smears: Selection of choice particles compared with various sodium hydroxide concentration techniques, Pub. Health Rep., 1949, *64*, 574.

(11) Drea, W. F.: The growth of human tubercle bacilli, H37, in synthetic medium with and without agar, J. Bact., 1940, *39*, 197.

CANCER DETECTED IN SURVEYS[1]

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INTRODUCTION

Tuberculosis and cancer of the lung have many similarities. Both have the power to kill, both develop insidiously, and both produce shadows on the chest roentgenogram which may be detected in surveys in advance of symptoms. Furthermore, roentgenographic shadows produced in their silent phase show great similarity. The two diseases differ in that the frequency of cancer of the lung is showing an alarming increase, whereas that of tuberculosis is declining. They differ also in that one is invariably fatal unless treated by excision in its localized form, while delay in treatment of the other does not always result in death. It seems important to consider the subject of cancer as a by-product of surveys for tuberculosis from the following points of view:

1. To emphasize that cancer has a detectable silent phase.
2. To consider difficulties in sorting out cases of tuberculosis and cancer during their silent phase on the basis of roentgenographic findings.
3. To recognize the necessity for streamlining the follow-up to avoid delays in the event of cancer.
4. To indicate steps that may be taken to ensure accuracy of diagnosis.

SILENT CANCER DETECTABLE IN SURVEYS

There is both presumptive and absolute evidence of the existence and detectability of silent forms of cancer of the lung. In accumulating data on ill cancer patients, it is possible at times to obtain for comparison roentgenograms taken at some period antedating symptoms. Some of these have shown an abnormal shadow corresponding in location to the one produced by the known cancer. It is reasonable to assume that the shadows in the early and late films represented photographic records of the same growth process.

There is absolute proof of the existence of cancer detectable in survey in its silent stage by virtue of the fact that cancers have been found upon surgical exploration in asymptomatic individuals. This experience is not uncommon in chest surgical centers. For example, in our clinic 145 patients have been explored for abnormalities discovered in surveys. Of these, 51 had lesions which proved to be neoplastic and 35, malignant (table 1). Watson (1) states that, of 104 cases of silent intrathoracic tumors at Memorial Hospital in New York City, 40 per cent proved to be malignant.

It is not at all surprising that tumors in their early developmental stage cast shadows on the roentgenogram. The majority of them originate in the larger

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bronchi, occlude the lumen, and cause segmental or subsegmental atelectasis. The obstructing growth need be but a few millimeters in size to produce secondary changes in the peripheral portion of the corresponding segment. These changes magnify the area of altered density many times, thus greatly increasing the likelihood of detection in survey work (figure 1). Regardless of whether or not

TABLE 1

Diagnosis Established by Intrathoracic Exploration for Lesions Detected in Surveys
Overholt Thoracic Clinic, 1938 to 1950

Tuberculosis	52
Cysts	27
Malignant tumors	35
Benign tumors	16
Diaphragmatic hernia	4
Intrathoracic thyroid	3
Others	8
Total	145

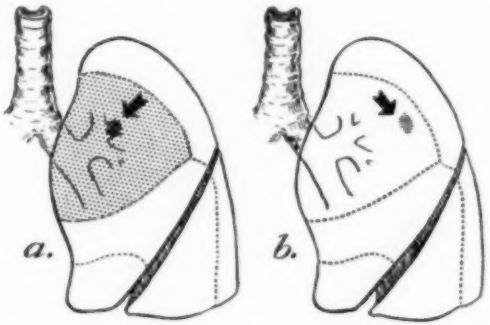


FIG. 1. Diagram to illustrate the reason why either peripheral or centrally placed tumors of small size should be detected in a survey film.

a. Centrally placed tumors arising in stem bronchi cast a shadow of segmental or subsegmental atelectasis. This shadow is, therefore, indirect; yet it greatly magnifies the actual size of the tumor.

b. In the periphery the tumor casts a direct shadow in contrast to the rarefied lung field. Lesions as small as 3 mm. in diameter may be distinguishable from normal markings.

the shadow of a small, centrally placed tumor itself is obscured by shadows of normal structures at the lung root, the magnified secondary changes in the lung field fortunately serve to attract attention to possible fatal danger.

In the event that the cancer has originated in a small bronchus or in a bronchiole, its situation will then be peripheral and in the part of the lung field of greatest contrast. The direct shadow of the tumor will be seen. According to Rigler (2), shadows of growths as small as three millimeters in diameter are detectable.

DIFFICULTIES IN DISTINGUISHING CASES OF CANCER AND TUBERCULOSIS

Difficulties experienced by doctors in the past in differentiating lung cancer from other conditions may be illustrated by citing experiences in our own clinic. In the past twelve years, 849 patients suffering from primary carcinoma of the lung have been studied. Of this number, 824 had symptoms when observed and had been under medical supervision for approximately six months on the average. This delay in detection resulted from trials of treatment for conditions incorrectly diagnosed. The most common erroneous diagnosis was tuberculosis. If abnormal shadows happened to be in the upper half of the lung field, the previous diagnosis was usually tuberculosis. If the shadow was in the lower lung field, the most likely diagnosis was bronchitis, bronchiectasis, or atypical or virus pneumonia. Examples of the various shadows produced by cancer and other

TABLE 2

Incidence of Possible Tumors Detected on 14 by 17 Chest Roentgenograms in Ten Surveys

GEOGRAPHIC LOCATION	NUMBER OF PERSONS EXAMINED	NUMBER OF POSSIBLE TUMORS	RATES PER 1,000 PERSONS EXAMINED
Savannah-Chatham County, Ga.	67,961	43	0.6
Gaston & Wayne Counties, N. C.	84,599	58	0.7
Milwaukee, Wis.	176,469	37	0.2
Minneapolis, Minn.	301,513	404	1.3
Washington, D. C.	439,927	373	0.8
Seattle-King County, Wash.	368,129	261	0.7
Tacoma, Wash.	72,703	32	0.4
Spokane, Wash.	106,526	67	0.6
Salt Lake Area, Utah	162,351	107	0.7
Total	1,780,178	1,382	0.8

conditions are shown in figures 2 to 8. An attempt has been made to arrange the pairs of roentgenograms in a manner which best illustrates some of the difficulties in differentiating cancer from other diseases. The majority are survey cases and, in these, all clinical tests except the abnormal area of density by roentgenogram were negative. In none of the cases selected did fluoroscopy or other views give additional clues to the cause of the abnormal shadows. The diagnosis in each instance was settled by surgical exploration.

THE YIELD FROM SURVEYS

According to Bloomquist (3), in ten city-wide surveys sponsored by the Public Health Service, 1,382 possible tumors were found in 1,780,178 persons examined. The yield was 0.8 per 1,000 (table 2). The final breakdown of this group of tumor suspects is not available as yet. However, in Minneapolis, Seattle, and Washington, the yield of primary pulmonary malignancy of all types (not including metastatic disease) was about 0.1 per 1,000 according to Hilbish (4).

Do these statistics give the true picture? There is reason to doubt seriously that the yield of primary cancer is as low as these reports indicate because: (*1*)

There are possibilities of error in identifying shadows. Undoubtedly some cases thought to be tuberculosis will turn out to be cancer. (*2*) There is a time lag in the follow-up. Unless suspect cases are studied promptly, the true value in saving of lives will be lost. Metastatic malignancy will modify the statistics. Some persons in whom verification has not been obtained clinically or at autopsy will die of cancer, and these cases will not be included in the statistics. (*3*) Patients with both cancer and tuberculosis are likely to be included only in the tuberculosis statistics. Some patients with an old tuberculous focus in the lungs may have this focus broken down by a malignant process, thus liberating tubercle bacilli in secretions from the lung.

Heretofore, the emphasis in mass survey programs has been on tuberculosis case finding. Facilities have not been adequate for following cases showing abnormalities other than tuberculosis. Delays were inevitable. In the recent Boston survey, the New England Heart Association and the Massachusetts Chapter of the American Cancer Society were invited to cooperate. The latter was represented on the Committee on Non-Tuberculous Lung Abnormalities, and special consideration was given to the matter of cancer detection. A recommendation was made to the effect that, when an abnormal lung shadow was found in men more than 40 years old, a special stamp, "Urgent—Cancer Suspect," be placed on the report. This was done to alert the patient's private physician to such a possibility and to encourage prompt investigation. Possibly the age limit should have been dropped to 35, and women should have been included.

The final breakdown of figures is not available but, of 528,941 satisfactory examinations, reports on 398 carried this warning stamp. At present, reports are complete on approximately one-third of these, and 36 proved cases of cancer have been found, 24 of which were primary.

ROENTGENOGRAPHIC EVIDENCE OF TUBERCULOSIS AND CANCER

Since the value of screening for asymptomatic tuberculosis is established and these programs are being undertaken, there is a real opportunity to find cancer in its silent stage as a by-product of these surveys. Furthermore, it is impossible to divorce consideration of the two diseases since the evidence obtained by roentgenographic examination in early tuberculosis and cancer is often indistinguishable. Suspects in both categories require further investigation. The only difference is the urgency of the study. It is suggested that, whenever chest roentgenographic programs are in progress, the follow-up of cases be geared to meet the necessity of identifying the two diseases accurately and promptly. This might be done as follows:

1. Invite agencies interested in cancer detection to cooperate and take over that phase of the follow-up.

2. Acquaint all physicians who read the survey films and all those who are to advise patients that it is difficult or impossible to differentiate the shadows of *silent* tuberculosis and silent cancer.

3. Accelerate the follow-up program in order to save valuable time in the event the survey film has revealed an early cancer.

FACTORS IN PROPER LABELING

It is quite obvious that the earlier in the life history of cancer of the lung that detection is made, the more difficult it is to obtain tissue for absolute verification. Additional studies are essential and should progress in the following order until the true diagnosis is settled:

1. Complete roentgenographic examination, including fluoroscopy, postero-anterior projections, and such supplementary films as are individually indicated. The oblique projections with the patient turned no more than 30° are most helpful. The lateral position, inspiration and expiration films, and/or laminagrams sometimes offer additional information.
2. Search for tubercle bacilli in sputum and gastric specimens. Negative findings may be used as presumptive evidence of cancer.
3. Cytological examination of sputum or bronchial washings.
4. Bronchoscopy and biopsy if a tumor is visible.
5. Surgical exploration with gross and microscopic examination of the tissue under suspicion.

The four preoperative examinations should be completed in less than a week and should be followed immediately by careful evaluation of all the data. Frequently the roentgenographic examination offers the only positive information. Negative cytology or bronchoscopy cannot be taken as proof of the absence of cancer. *Roentgenographic evidence of pulmonary abnormality establishes no diagnosis.* To illustrate this point, figures 2–8 show seven pairs of abnormal chest roentgenograms. Symptoms were either noncontributory or absent. Let the reader attempt diagnosis before turning to the key to diagnosis at the end of the article.

All patients with abnormal shadows which cannot be adequately explained on another basis should have the benefit of surgical exploration. To date, there is no cure for a primary lung cancer except its removal. Our experience shows that, if the patient waits for symptoms and if the delays that follow in the average case are added to this time lost, approximately 90 per cent of the lesions have by that time extended to structures outside the lung (5). The possibility of cure, therefore, is limited to a meager 10 per cent in the symptomatic stage of the disease. To explore and to carry out excisional treatment during the silent phase will set treatment ahead by months or years. In our clinic when prompt treatment has followed discovery of cancer by survey, all lesions have been resectable and 75 per cent have shown no evidence of lymphatic spread. All patients in this group are still living.

SUMMARY

1. Cancer of the lung has a silent phase, and in this phase a cancer is more likely to be curable than one producing symptoms.

2. A small cancer originating in the periphery casts a direct shadow. A small cancer originating in a segmental bronchus produces a magnified secondary shadow. In either situation these shadows are visible in survey films.

3. Shadows of silent cancer and silent tuberculosis look alike; numerous difficulties in differentiation complicate accurate identification.

4. All persons suspected of having cancer must be differentiated promptly, for delays in diagnosis spell disaster.

5. Of all sites for internal cancer, the lung should be the most favorable from the standpoint of early detection for these reasons:

(a) Mass screening for tuberculosis automatically screens for cancer.

(b) Multiple tests are available to aid in differentiation between tuberculosis and cancer.

(c) Surgical exploration and removal are safe and effective when promptly applied in silent cancer.

SUMARIO

Cáncer Descubierto en las Encuestas

1. El cáncer pulmonar tiene una fase silenciosa, en la cual un cáncer es más susceptible de mostrarse curable que sintomático.

2. Un cáncer pequeño partido de la periferia lanza una sombra directa, en tanto que si procede de un bronquio segmentario produce una imagen secundaria ampliada. En uno u otro sitió, esas sombras son visibles en las películas de encuesta.

3. Las imágenes producidas por el cáncer silencioso y la tuberculosis silenciosa tienen aspecto semejante; numerosas dificultades en la diferenciación complican la identificación exacta.

4. En todas las personas en que se sospecha cáncer la diferenciación debe ser rápida, pues las demoras en el diagnóstico resultan desastrosas.

5. De todos los asientos del cáncer visceral, el pulmón debe ser el más propicio desde el punto de vista del descubrimiento temprano, por las siguientes razones:

(a) El despistaje colectivo de la tuberculosis despista automáticamente el cáncer.

(b) Hay a mano muchas pruebas para ayudar a diferenciar entre tuberculosis y cáncer.

(c) La exploración y la extirpación quirúrgicas son inocuas y eficaces si se aplican prontamente en el cáncer silencioso.

REFERENCES

(1) Watson, W. S.: Personal communication.

(2) Rigler, L. G.: Roentgen examination of the chest: Its limitations in the diagnosis of disease, J. A. M. A., March 18, 1950, *142*, 773.

(3) Bloomquist, E. T.: Personal communication.

(4) Hilbish, T. F.: Personal communication.

(5) Overholt, R. H., and Schmidt, I. C.: Silent phase of cancer of the lung, J. A. M. A. November 19, 1949, *141*, 817.

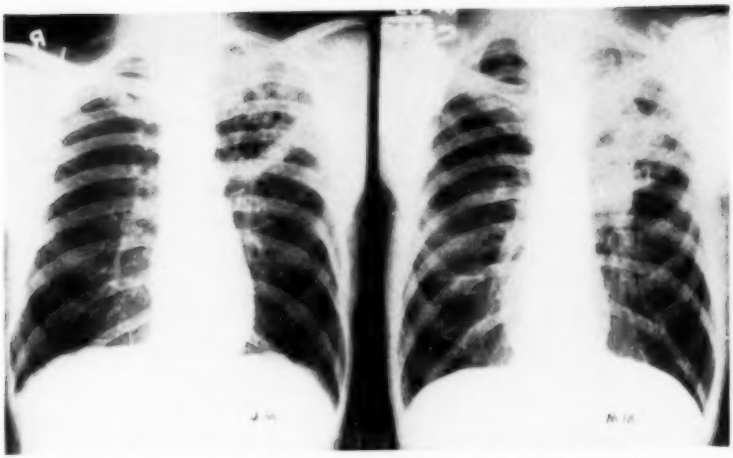


FIG. 2 (Left) J. M., male, age 39. (Right) M. MacM., male, age 56.

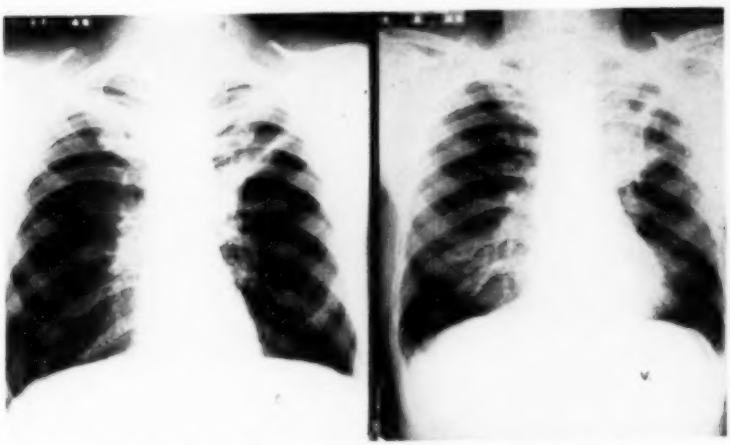


FIG. 3 (Left) P. G., male, age 60. (Right) C. V., male, age 50.

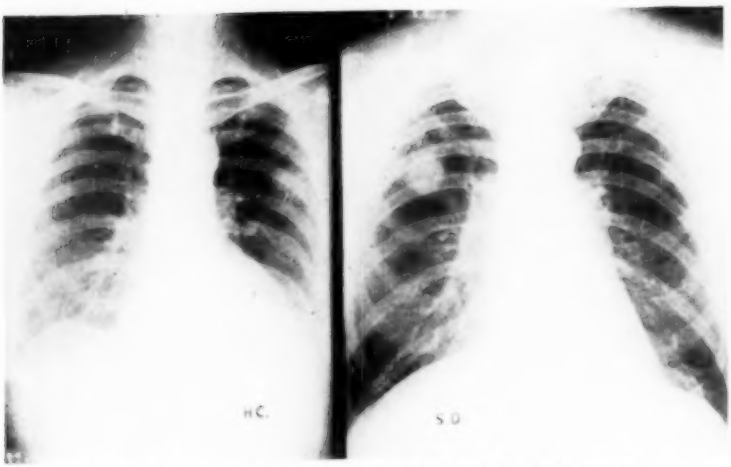


FIG. 4 (Left) H. C., female, age 66. (Right) S. D., male, age 61.

FIG. 5 (Left) M. P., female, age 45. (Right) L. H., female, age 26.

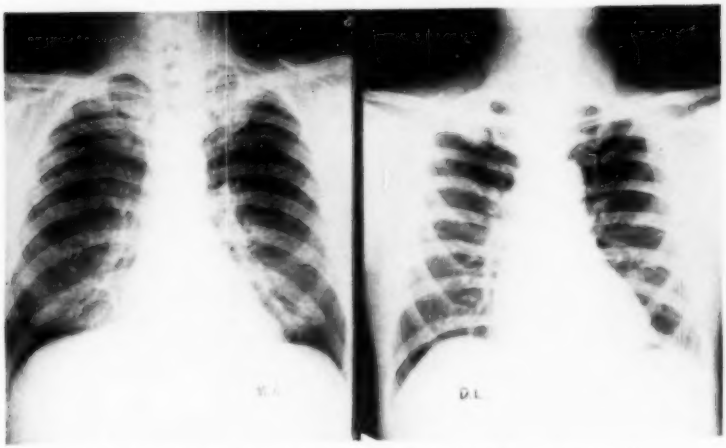


FIG. 6 (Left) M. A., male, age 45. (Right) D. L., male, age 48.

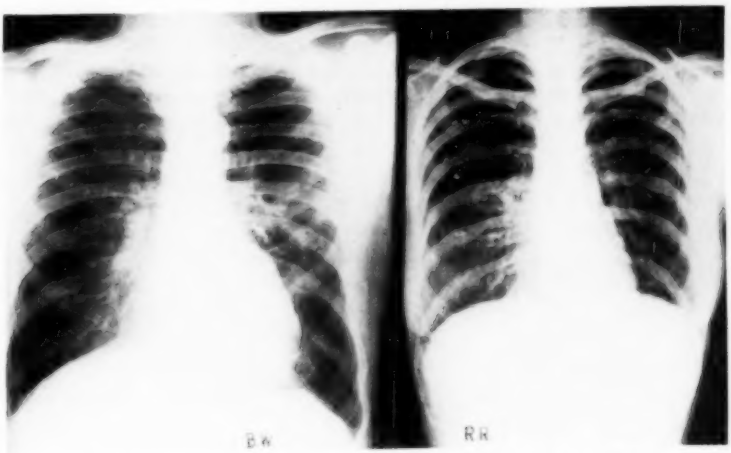


FIG. 7 (Left) B. W., male, age 64. (Right) R. R., female, age 29.

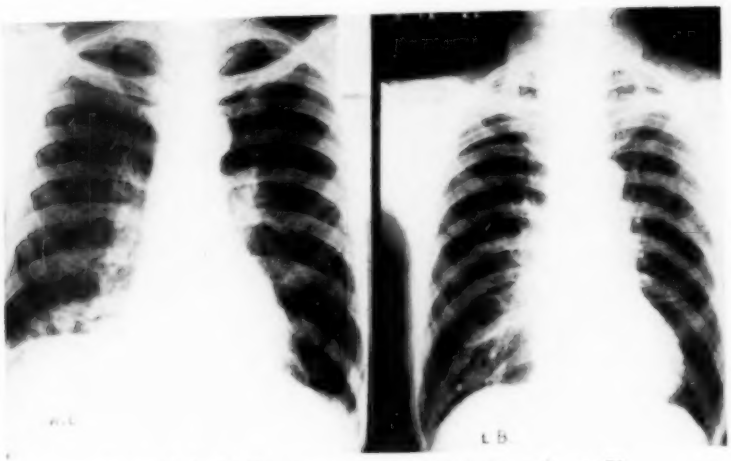


Fig. 8 (Left) W. O., male, age 34. (Right) L. B., male, age 73.

KEY TO DIAGNOSIS OF ROENTGENOGRAMS

Twelve of the 14 cases were verified by surgical exploration and excision, the exceptions being figure 2, left, and figure 7, right. All cancers were primary in the lung. The diagnoses are as follows:

Fig. 2. Left—Tuberculosis	Right—Cancer, epidermoid, Grade II
Fig. 3. Left—Lung abscess	Right—Cancer, simplex
Fig. 4. Left—Adenocarcinoma	Right—Tuberculosis
Fig. 5. Left—Adenocarcinoma	Right—Tuberculosis
Fig. 6. Left—Cancer, unclassified	Right—Cancer, simplex
Fig. 7. Left—Cancer, epidermoid, Grade II	Right—Lung abscess
Fig. 8. Left—Bronchiectasis	Right—Cancer, epidermoid, Grade II

MASS SURVEYS AS CASE-FINDING TECHNIQUES FOR PULMONARY NEOPLASMS[1, 2]

KATHARINE R. BOUCOT

(Received for publication April 27, 1950)

Introduction

Although mass roentgenographic surveys were originally designed for tuberculosis case finding, it is inevitable that a certain number of cases considered as possible tuberculosis should ultimately be proved to be malignant tumors. In view of the low mortality of pneumonectomy and of the hopeless prognosis of untreated carcinoma of the lung, it seems appropriate to consider whether or not surveys can make a significant contribution to the case finding of pulmonary neoplasms.

The Philadelphia Tuberculosis and Health Association surveys recapitulate the experience of many pioneer surveys. There was no systematic follow-up in the early period. In the next period, follow-up was routine and meticulous on cases of possible tuberculosis but absent on cases of possible neoplasms. At present both tuberculosis and neoplasm are emphasized equally. This evolution came as the result of an increasing awareness of the problem as reports of neoplasm were received on cases being followed only because tuberculosis had been suspected. A casual list of such cases, kept over a seven-month period, disclosed 80 instances of proved or suspected neoplasms, including benign tumors as well as primary and metastatic carcinomas (1).

Subsequently, we reviewed the follow-up on tuberculosis suspects among 156,920 individuals surveyed between May 1, 1945 and March 31, 1948. In this period of thirty-five months, there were 34 proved malignant tumors, a prevalence of one in every 5,000. We reviewed separately that segment of this group which had been surveyed at our Central Unit to which come a higher percentage of individuals with symptoms. The prevalence of neoplasm encountered among these 26,209 individuals was one in every 2,000. Since we believed that these were minimal figures, we inaugurated on April 1, 1948 a case-finding and follow-up program for neoplasm identical with that in operation for tuberculosis. It is the purpose of this paper to illustrate the various categories utilized in interpretation of photofluorograms in this study, and to present some of the results of the study as well as certain of the problems encountered.

Interpretation of Photofluorograms

All photofluorograms are read as "suspect neoplasm" in which there are present parenchymal mass, emphysema suggesting obstruction, mediastinal enlarge-

[1] From the Philadelphia Tuberculosis and Health Association.

[2] Presented before the Medical Session, as part of the symposium on *Mass Chest X-ray Surveys, Part I*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 27, 1950.

ment, atelectasis, soft infiltration, or cavity associated with mediastinal involvement or shift. Typical examples of these categories follow.

PARENCHYMAL MASS

Case 1. N. D. was a 52-year-old white male whose photofluorogram on May 23, 1948 (figure 1) revealed a mass above the right hilum. He had had blood-streaked sputum for six weeks, occasional chest pain, and fever. Hospitalization was refused. A second photofluorogram on December 27, 1948 revealed marked progression. He then had bloody diarrhea, weight

FIG. 1. Case 1. May 23, 1948. Mass above right hilum. Patient refused hospitalization. Biopsy of supraclavicular node revealed metastic carcinoma from the bronchus. Death occurred April 4, 1949 following generalized convulsions.

loss of 9 pounds over the previous three months, and occasional blood-streaking of the sputum. On February 16, 1949 roentgenograms revealed atelectasis of the upper lobe of the right lung associated with spread throughout both lungs. The patient was admitted to Philadelphia General Hospital on March 23, 1949 following generalized convulsions. Examination of a supraclavicular node obtained by biopsy revealed metastatic carcinoma from the bronchus. Death occurred April 4, 1949.

EMPHYSEMA SUGGESTING OBSTRUCTION

Case 2. F. B., a 56-year-old Negro male, was referred by his private physician for a photofluorogram on July 26, 1948 (figure 2). Infiltrations associated with obstructive emphysema were present in the right mid-lung field, as well as infiltrations at the left apex. In view of two negative examinations of sputum, the large film was interpreted as "minimal tuberculosis of indeterminate activity." Observation was continued until May 1949, when

bronchoscopy was performed. There was slight medial compression of the right main bronchus just below the carina, but no carcinoma cells were found. (Subsequently, one sputum examination was positive for tubercle bacilli.) Because cough and dyspnea grew worse and there was some loss of weight, he was admitted to Temple University Hospital on January 17, 1950. At this time there was atelectasis of the upper lobe of the right lung. Biopsy was performed at bronchoscopy, and a diagnosis of bronchogenic carcinoma was made on the tissue obtained. Pneumonectomy was attempted but cardiac arrest occurred during the procedure and, although the patient was resuscitated, it was deemed unwise to

FIG. 2. Case 2. July 26, 1948. Localized emphysema in upper half of right lung. Infiltrations in right mid-lung field and left apex. Bronchogenic carcinoma proved by histologic examination of specimen obtained at bronchoscopy. Sputum culture also positive for tubercle bacilli on ten occasions. Thoracotomy revealed inoperable carcinoma.

attempt resection. Anaplastic carcinoma involved the pleura. Cultures of ten sputum specimens were subsequently positive for tubercle bacilli. The patient was discharged on March 15, 1950 with inoperable bronchogenic carcinoma and active tuberculosis.

Comment: This case illustrates one of the major problems of follow-up, i.e., delay in cases of nontuberculous disease while the diagnosis of tuberculosis is being considered. Even when positive sputum is present, if there is a question of possible malignancy diagnostic studies should be viewed as an emergency.

MEDIASTINAL ENLARGEMENT

Case 3. J. S. (1), a 70-year old white male, had been attending a diabetic clinic for two years. On April 12, 1946 he had a photofluorogram which was interpreted as "suspect neo-

plasm: well-defined right mediastinal mass" (figure 3). The patient continued to be asymptomatic until June when he developed blood-streaked sputum. He was hospitalized, developed paralysis of the right diaphragm, and died on August 14, 1946. Autopsy confirmed the survey diagnosis of bronchogenic carcinoma.

Comment: This case exemplifies the ironical situation of a cooperative patient developing inoperable bronchogenic carcinoma while being regularly checked for a chronic illness.

ATELECTASIS

Case 4. J. N., a 59-year-old white male, was referred to the Central Unit on February 21, 1949 by his private physician. He complained of right chest and shoulder pain of six weeks' duration, but denied cough, hemoptysis, or weight loss. The photofluorogram revealed atelectasis of the right middle lobe (figure 4). The patient was admitted to the hospital of the University of Pennsylvania on March 6, 1949, had a right pneumonectomy for bronchogenic carcinoma, and was discharged as improved on April 1, 1949. Despite the short period of symptoms and prompt surgical intervention, the patient died in June 1949.

SOFT INFILTRATION OR CAVITY ASSOCIATED WITH MEDIASTINAL INVOLVEMENT OR SHIFT

Case 5. J. P., a 68-year-old white male, was referred by his private physician for examination on December 31, 1947. He had had hemoptysis for one month. The photofluorogram revealed a cavity in the left mid-lung field in the center of a dense mass suggestive of neoplasm (figure 5). The man was hospitalized on March 28, 1948 after several unsuccessful efforts to convince him of the need for therapy. Left pneumonectomy was done on April 25, 1948, but he died of a massive pulmonary hemorrhage one year after surgery.

Results of Surveys

Prevalence of neoplasm: In a survey of 40,607 apparently healthy workers in industry studied between April 1, 1948 and March 31, 1949, the prevalence of neoplasm was 0.14 per cent. This represents a prevalence about five times that found by Gould (2) in a survey of 442,252 individuals in 1944. Of the 18,633 satisfactory photofluorograms exposed at our Central Unit during this same period, 56, or 0.30 per cent, were read as "suspect neoplasm." During the subsequent ten to twenty months, histologic diagnosis of neoplasm has been obtained in 16 of these suspects, while there have been 8 additional proved cases found in those suspected only of having tuberculosis. Thus, the prevalence of proved cancer was 0.13 per cent. Three of these were metastatic, 2 from the breast, and one from an unknown primary site. One case proved to be leukemia and another Hodgkin's disease. The remaining 19 were primary bronchogenic carcinomas. Of these primary cancers, only 3 occurred in females, so that the ratio of male to female was 5 to one. The youngest was 47 years old. Two benign tumors were found in this group, a thymoma and a hamartoma, both occurring in young women in their twenties.

While surveys were planned only for apparently healthy individuals, an increasing emphasis on hospital and community surveys has resulted in the inclusion of a large number of persons with symptoms. This trend should be recognized despite the fact that miniature photofluorograms are inadequate as radiologic studies on those with symptoms. It seems wise to guard against sending reports

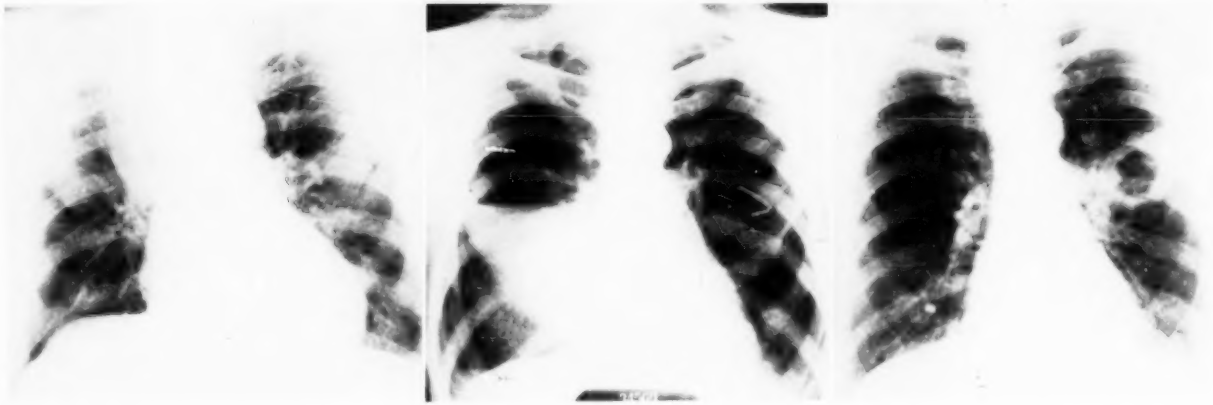


FIG. 3. Case 3. (Left) April 12, 1946. Mediastinal mass on right. Patient asymptomatic until June. Death occurred August 14, 1946. Autopsy revealed bronchogenic carcinoma.

FIG. 4. Case 4. (Center) February 21, 1949. Atelectasis of right middle lobe. Right pneumonectomy for bronchogenic carcinoma March 1949, but death occurred in June 1949.

FIG. 5. Case 5. (Right) December 31, 1947. Mass with cavity in left mid-lung field adjacent to hilum. Left pneumonectomy April 25, 1948. Death occurred April 1949 from massive pulmonary hemorrhage.

of "negative" on individuals with symptoms. Toward this end, our technicians record the response to four questions regarding cough, chest pain, hemoptysis, and weight loss. This information is available to the physician who reads the films at the time of the interpretation. Individuals with symptoms are interviewed and referred for study whether or not significant abnormalities are found in the photofluorogram (3).

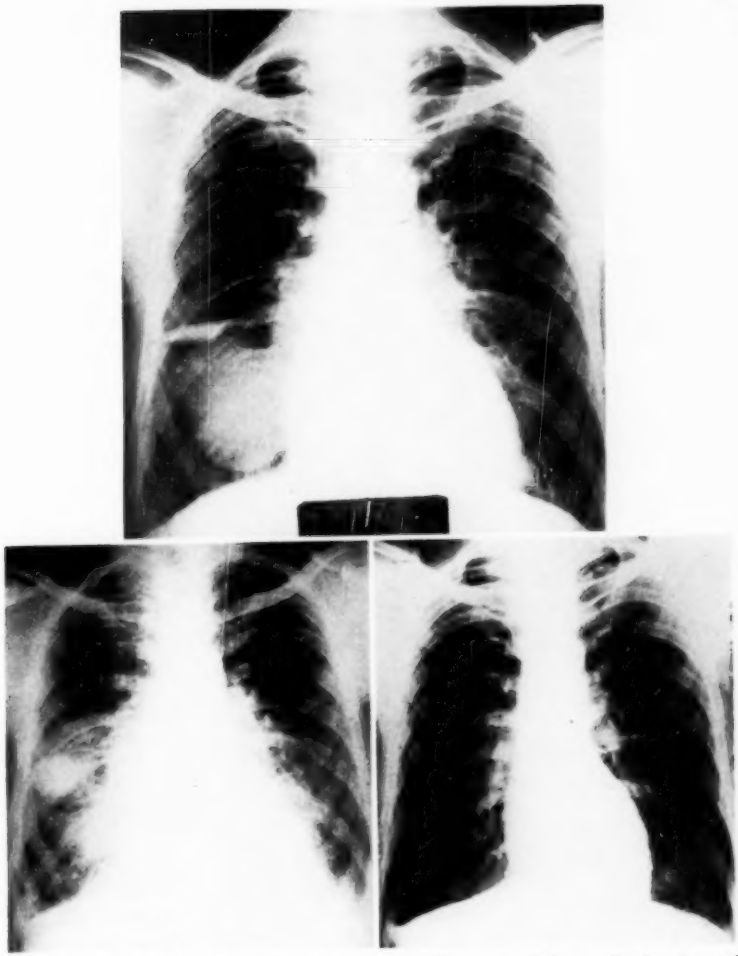
A more detailed statistical analysis was conducted on 4,004 individuals who reported to the Central Unit during the first three months of 1949. Thirty per cent had symptoms. Twenty-three, or 0.58 per cent, had photofluorograms interpreted as "suspect neoplasm." This is twice the figure for the whole period of this study and may be due to a higher index of suspicion as the importance of the situation became apparent. Of those with symptoms, 1.4 per cent were classified "suspect neoplasm" in contrast to 0.2 per cent of those without symptoms.

Of the 16 cases read "suspect neoplasm" on which follow-up information is available, 5 of the patients had proved bronchogenic carcinoma. An additional 2 cases were found among those suspected of having only tuberculosis, making a total of 7 proved lung cancers, or 0.2 per cent, approximately the same figure obtained on the larger group previously discussed. All 7 neoplasms, however, were in men over 45 years old and, since there were only 286 men in this age group, the prevalence of proved lung cancer in men over 45 years of age was 2.4 per cent. This figure is startling even in a survey which includes so many people with symptoms. Studies are now in progress on a larger group. Of the 7 proved cases, all but one patient had symptoms at the time of the photofluorogram. Thus, the prevalence is 4.7 per cent in the group of 126 men over 45 years of age who had symptoms, while it is 0.6 per cent for the group of 160 without symptoms.

The survey reading of "suspect neoplasm" is inadequate without proper follow-up. Any persistent pulmonary infiltrations not definitely diagnosed as tuberculosis should be considered possibly neoplastic, especially in men over 45 years of age (1). This concept should be as acceptable as the one by which all pleural effusions are considered tuberculous until proved otherwise. There should be no resentment when patients whose photofluorograms strongly suggest neoplasm are ultimately diagnosed otherwise. The following cases illustrate in part the problem of differentiating benign from malignant appearances.

Case Reports

Case 6. F. H. (4) a 53-year-old white male, had a photofluorogram on his own accord on December 7, 1948 (figure 6). Hospitalization was recommended because of the presence of a mass near the right cardiophrenic angle associated with a small amount of fluid in the interlobar fissure. The hospital admission film of January 5, 1949 (figure 7) revealed a mass in the right mid-lung field and no mass near the right heart border. In view of the obvious cardiac enlargement and history of exertional dyspnea, it was recognized that this was an example of "vanishing tumor" (localized interlobar pleural effusion associated with congestive heart failure). Mercurial diuretics were administered with prompt complete absorption of the pleural fluid (figure 8).

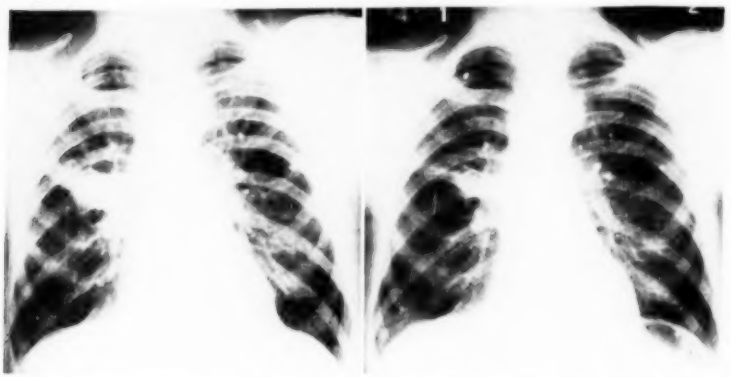


FIGS. 6, 7, 8. Case 6. (Top) December 7, 1948. Mass near right cardiophrenic angle; small amount of fluid in interlobar fissure. Hospitalization recommended. (Lower left) January 5, 1949. Hospital admission film. Rounded mass right mid-lung field. Mass described as present December 7, 1948 not visible; heart enlarged; pulmonary congestion present. Diagnosis: "vanishing tumor." (Lower right) Absorption of fluid following administration of mercurial diuretics. Note clearing of congestion and decrease in heart size.

Case 7. S. W., a 66-year-old white male, had a photofluorogram on March 8, 1948 interpreted as strongly suggestive of neoplasm (figure 9). He stated that he had cough, not only productive of bloody sputum but of pieces of lung tissue. He was admitted to Temple University Hospital on June 17, 1948. Examination of bronchial secretions was positive for

tubercle bacilli but no tumor cells were found. He improved on a regimen of rest and is now well and working (figure 10).

Of the 19 proved bronchogenic carcinomas found in 18,633 individuals surveyed during one year, 13 were discovered through photofluorography. Fifteen persons died within 10 to 20 months after their photofluorograms; only 3 were suitable for resection. Thus, either we are too conservative in our film reading, we fail to survey individuals often enough or, conceivably, early operable carcinoma of the lung is rarely detectable by survey. Probably all three factors are involved. In an effort to evaluate the situation, the miniature films of the proved cases were reviewed. The lesions fell into six categories, with one or more of the



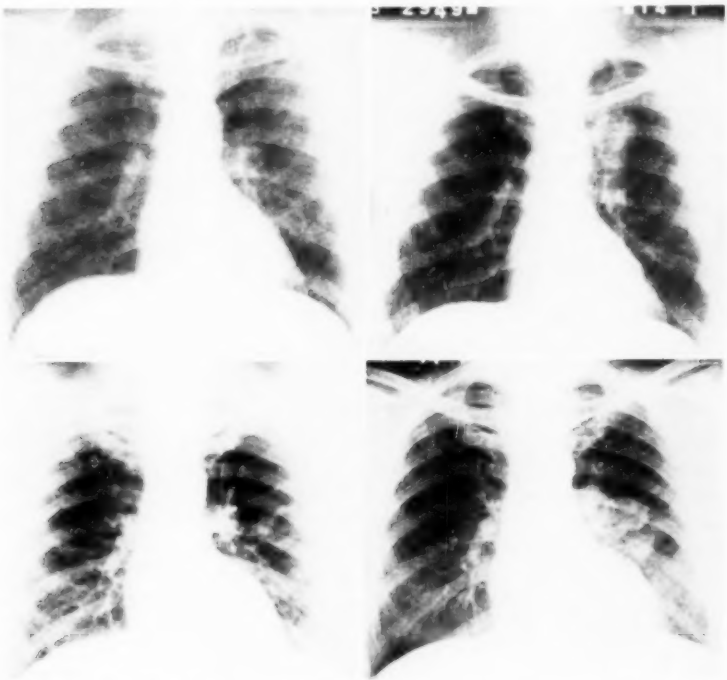
FIGS. 9 and 10. Case 7. (Left) March 8, 1948. Infiltrations from right hilum strongly suggestive of neoplasm. Bronchoscopy and examination of bronchoscopic secretions revealed no evidence of tumor, but bronchial secretions were positive for tubercle bacilli. Patient coughed up bloody sputum and fragments of lung tissue. (Right) March 18, 1950. Regression. Sputum negative. Patient asymptomatic.

following characteristics: (*1*) presence of a mass, (*2*) mass with cavity, (*3*) atelectasis, (*4*) rib erosion, (*5*) dense infiltrations with "solid" appearance, (*6*) massive pleural effusion not associated with evidence of cardiac decompensation.

All 8 of those with a definite mass had been read as "suspect neoplasm." Similar reading was made of the one case with a mass in which there was a rarefaction, the one with rib erosion, and the one with massive left pleural effusion without evidence of cardiac decompensation. Three of the 4 cases of atelectasis were interpreted as "suspect neoplasm." The case missed was not altogether obvious on the miniature film. The worst errors, however, were in the 4 cases of dense infiltrations. Only one of the 4 in this category was suspected of having a neoplasm. The one properly interpreted really had a suggestion of mass as well as infiltrations. It is in this group we might read more boldly the suggestion of neoplasm.

Frequency of examination: The optimal time interval between examinations

is undetermined. It is known, however, that cases of inoperable carcinoma have been encountered within two years after a "negative" photofluorogram.



FIGS. 11 and 12. Case 8. (Upper left) February 24, 1947. Negative. (Upper right) March 29, 1949. Dense infiltrations radiating from left hilum. Although hospitalized immediately, patient was found to have inoperable bronchogenic carcinoma.

FIGS. 13 and 14. Case 9. (Lower left) February 21, 1947. Infiltrations left third interspace. (Lower right) February 24, 1948. Three rounded masses at left hilum. Hospitalization refused. Asymptomatic at this time. Death occurred September 19, 1948 following development of headache, psychosis, hemiparesis. Autopsy revealed squamous cell carcinoma of the bronchus with cerebral metastases.

Case Reports

Case 8. A. D., a 57 year-old white male diabetic, had a negative photofluorogram in a survey on February 24, 1947 (figure 11). On March 29, 1949 (figure 12) he reported to the plant physician that he had been hoarse for two weeks. No other symptoms were present. He was referred that day to our Central Unit where a photofluorogram was interpreted as "suspect neoplasm" because of dense infiltrations above the left hilum. He was hospitalized the day the film was read. Laryngoscopy revealed paralysis of the left vocal cord and he was thus deemed inoperable. He received X-ray therapy and was able to work intermittently until pain from metastases became intolerable. He was admitted to the Naval Hospital on October 3, 1949 where he died on January 31, 1950.

Apparently innocuous lesions have been read erroneously as clinically insignificant; resurvey one year later has revealed inoperable cancer which, in retrospect, should have been suspected in the earlier film.

Case 9. J. B., a 47-year-old white male, on February 21, 1947 had the routine photofluorogram required annually on all Philadelphia foodhandlers (figure 13). It revealed infiltrations in the left third anterior interspace. In the absence of symptoms, these were thought to represent old tuberculosis of no significance at the time. No serial examinations were made, but one year later at the routine examination on February 4, 1948 (figure 14), three large rounded masses were plainly visible in the region of the left hilum. Unfortunately, this patient refused hospitalization because he had no symptoms. Seven months later, in September 1948, he was admitted to a hospital because of headache. He became psychotic and developed a left hemiparesis. He was transferred to Philadelphia General Hospital, where he died on September 19, 1948. Autopsy revealed squamous cell carcinoma of the bronchus with cerebral metastases.

Because of the experience with these and similar cases, roentgenographic examination every six months is recommended for men over 45 years of age where facilities are available.

Summary

Mass surveys are suitable case-finding techniques for pulmonary neoplasms provided they are interpreted with a high index of suspicion, are recognized as screening in nature, and are followed promptly by adequate diagnostic studies. Because of the high prevalence of lung cancers among men over 45 years of age, this particular group should be checked every six months wherever possible. In the clinical evaluation of survey cases with significant findings, persistent pulmonary infiltrations not definitely diagnosed as tuberculous should be considered possibly malignant.

Sumario

Las Encuestas Colectivas como Técnicas para el Descubrimiento de Casos en las Neoplasias Pulmonares

Las encuestas colectivas resultan adecuadas como técnicas de descubrimiento de casos en las neoplasias pulmonares con tal que se interpreten con un máximo de suspicacia, se reconozca su naturaleza despistadora y vayan seguidas prontamente de estudios apropiados de diagnóstico. Las radiografías torácicas periódicas son convenientes para todas las personas adultas, pero dada la frecuencia del cáncer pulmonar entre los varones de más de cuarenta y cinco años, ese grupo en particular debe ser comprobado cada seis meses, siempre que sea posible. En la justipreciación clínica de los casos que muestran hallazgos indicativos en las encuestas, las persistentes infiltraciones pulmonares que no se diagnostican positivamente como tuberculosas deben considerarse como posiblemente malignas.

REFERENCES

(1) Boucot, K. R.: Mass surveys in case-finding techniques for pulmonary neoplasm, J. Am. M. Women's A., 1948, *3*, 485.

(2) Gould, D. M.: Nontuberculous lesions found in mass X-ray surveys, J. A. M. A., 1945, *127*, 753.

(3) Boucot, K. R., and Cooper, D. A.: A critical evaluation of mass roentgen surveys, J. A. M. A., 1950, *142*, 1255.

(4) Gefter, W. I., Boucot, K. R., and Marshall, E. W.: Localized interlobar effusion in congestive heart failure: "Vanishing tumor of the lung", Circulation, 1950, *2*, 336.

ASYMPTOMATIC AND CIRCUMSCRIBED LESIONS OF THE CHEST

WALTER F. BUGDEN

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INTRODUCTION

With the increasing use of roentgenographic examination of the chest in mass surveys, thoracotomy is being done with increasing frequency for the so-called "silent" lesion of the chest and for circumscribed lesions, either symptomatic or "silent." Because of the reluctance of many physicians to refer patients with such lesions for thoracotomy and surgical removal, reiteration of principles advanced by thoracic surgeons is justified and desirable. The purpose of this report is to present observations made in 8 patients with "silent" or circumscribed lesions of the chest, with the thought that the events in these cases clarify in some measure the attitude of the thoracic surgeon.

Case Reports

Case 1 (figure 1). The patient was a 45 year old white male who had no complaints or symptoms. Following a routine roentgenographic examination of the chest by his company he was told that he had a tumor in his right chest. An operation was advised and was performed. A large parasternal hernia containing omentum was found. The postoperative course was uneventful, and the patient has remained well for three years.

Case 2 (figure 2). This 8 year old white girl had a chest roentgenogram taken because of contact with a case of tuberculosis. The examination revealed what appeared to be a large tumor in the right chest. At operation a huge ganglioneuroma, which apparently arose from the seventh intercostal nerve, was removed. Three weeks later a laminectomy was performed by a neurosurgeon and a 3 cm. dumbbell type of tumor was removed from the spinal canal. The patient has been followed for three years and is well.

Case 3 (figure 3). The patient was a 60 year old white male who visited his local doctor because of slight malaise and some weight loss despite a good appetite. He had a mild chronic cough which he considered to be a "cigarette" cough. A chest roentgenogram revealed a small rounded lesion in the right upper lobe. Bronchoscopic examination was negative. At operation the right lung was removed and the pathologist reported the lesion to be a squamous cell carcinoma. The patient has been well for four years.

Case 4 (figure 4). This 58 year old female had a panhysterectomy in 1943 for adenocarcinoma of the uterus. In October 1948 she had several small hemoptyses. Chest roentgenograms revealed a circumscribed lesion in the left upper lobe. Operation was advised and a lobectomy was performed. The pathologist reported the lesion to be metastatic adenocarcinoma, the same as the lesion of the uterus. The patient is well eighteen months after the operation.

Case 5 (figures 5a and b). The patient was a 42 year old white male who complained of a cough and some malaise for several months before his first chest roentgenogram. The film revealed a small, round lesion beneath the left clavicle which was said to be "probably a tuberculoma." The patient was again examined roentgenographically two months later, at which time he was very dyspneic. He had rejected the advice to have a recheck roentgeno-

gram in three weeks.) The second film was interpreted as showing a slight increase in size of the lesion and, in addition, a pericardial effusion. A pericardiocentesis was done and

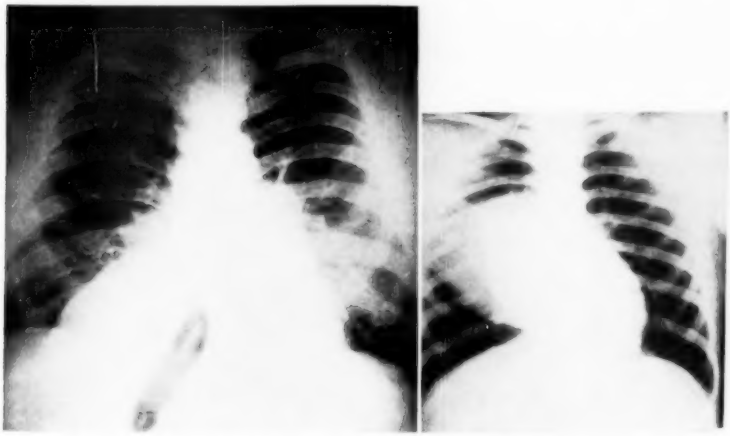

FIG. 1, Case 1. (Left) Parasternal hernia.
FIG. 2, Case 2. (Right) Ganglioneuroma of seventh intercostal nerve.

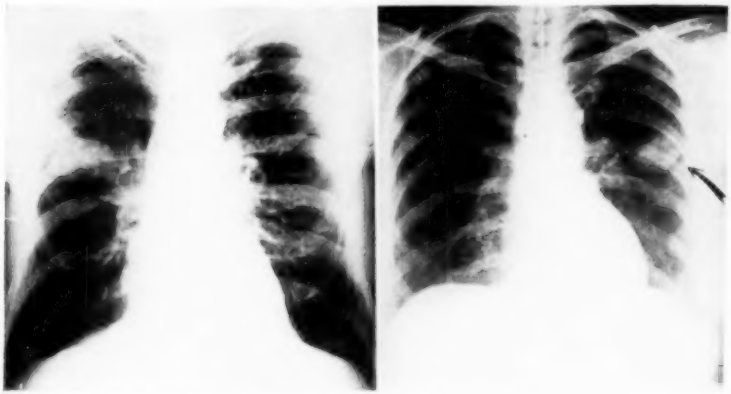

FIG. 3, Case 3. (Left) Squamous cell carcinoma, right upper lobe.
FIG. 4, Case 4. (Right) Metastatic adenocarcinoma of left upper lobe. Primary tumor in uterus had been removed five years previously.

carcinoma cells were found in the bloody fluid aspirated from the pericardium. The patient expired three weeks later. Autopsy revealed a bronchogenic carcinoma of the left upper lobe with extensive metastases to the heart.

Case 6 (figure 6). This 38-year-old Negro male had a roentgenogram of the chest taken

because of some malaise, but no cough. The examination revealed a large, rounded mass in the right chest, interpreted as probably being a ganglioneuroma or neurofibroma. At operation a squamous cell carcinoma was found, and a right pneumonectomy was performed. The patient died twenty-four hours postoperatively of pulmonary edema, cause undetermined. (During surgery there was an eight-minute period of cardiac arrest which was treated by manual cardiac massage, with subsequent return to normal rhythm.)

Case 7 (figure 7). This patient was a 19-year-old student nurse who was hospitalized because of vague, right upper abdominal pain, which had been considered to be subacute cholecystitis. Roentgenograms of the chest revealed a small lesion in the right costophrenic angle with an area of questionable infiltration in the right second interspace. At operation

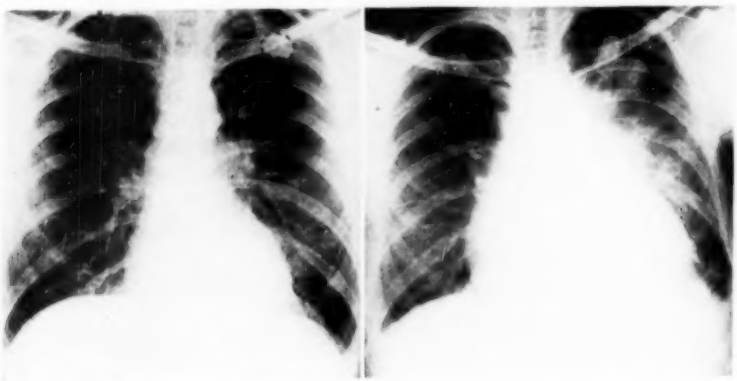

FIG. 5, Case 5.

a. (Left) Roentgenogram of chest taken at onset of symptoms. The lesion at left apex was thought to be tuberculosis.

b. (Right) Appearance two months later. Slight increase in the lesion previously noted, as well as appearance of pericardial effusion. Final diagnosis: bronchogenic carcinoma with metastases to heart.

this proved to be an acute tuberculous lesion with extensive pleuritic adhesions. A wedge resection was done and streptomycin therapy was initiated. The patient made an uneventful recovery. She was kept on strict bed rest for six months, and has now returned to work.

Case 8 (figure 8). This patient was a 24-year-old male student. He was told he had a chest lesion following a routine roentgenogram of the chest. The lesion was in the middle mediastinum and exploration was advised. A large bronchogenic cyst was removed from the mediastinum with some difficulty because of dense adhesions to the right auricle and esophagus, and tracheal bifurcation. He has remained well for two years postoperatively.

DISCUSSION

The view is often taken by the physician and the roentgenologist that chest lesions which are silent or circumscribed should be left alone and merely observed for signs of growth or the intervention of symptoms. Too often, however, a period of watchful waiting will become a fatal latent period. It is recognized that malig-

nant lesions may metastasize while still small, even though local growth is not apparent. Thus, the period of "conservatism" may be the direct cause of prolonged illness or even death. The physician who recalls one similar patient who

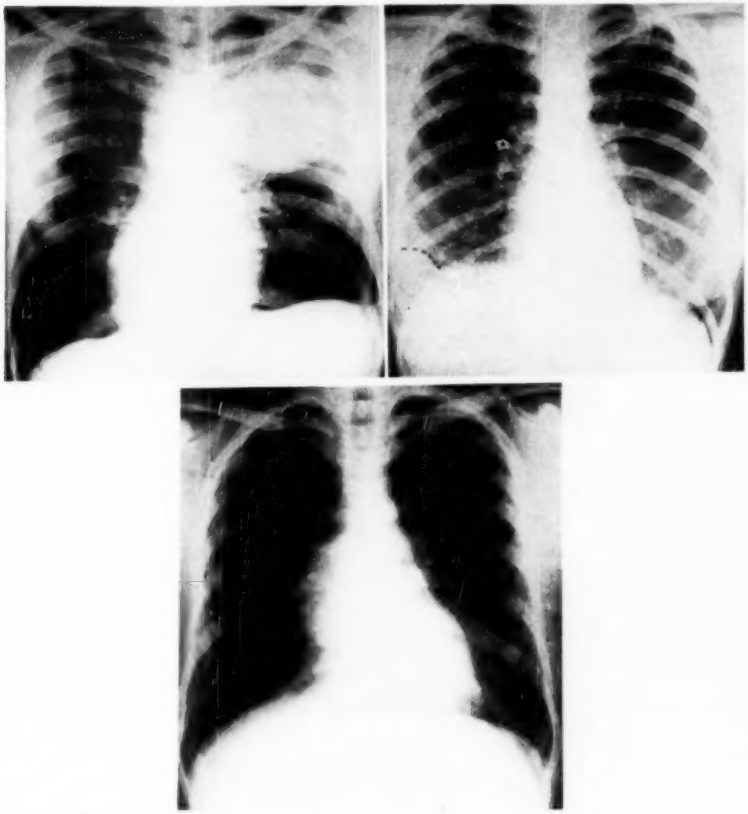

FIG. 6, Case 6. (Upper left) Squamous cell carcinoma of right lung.

FIG. 7, Case 7. (Upper right) Preoperative roentgenographic appearance of lung, showing small lesion in right costophrenic angle. At operation found to be an acute, caseous lesion of tuberculosis.

FIG. 8, Case 8. (Bottom) Bronchogenic cyst.

went untreated and remained well for many years is particularly refractory to the aggressive viewpoint. It is undoubtedly true that many such patients have done well with merely observation over the years, but many more have gone on to die, undiagnosed and untreated.

Because we often cannot make an accurate diagnosis of the true pathologic

nature of the lesion, we must be alert to the strong possibility of malignancy, or to the existence of a benign tumor which at a later date, may produce serious complications, such as hemorrhage or suppuration. We are often forced to thoracotomy and biopsy to establish the diagnosis. To quote Effler, Blades, and Marks (1), with whom virtually all thoracic surgeons are in accord: "It is our belief that accurate, pre-operative diagnosis of an asymptomatic lung tumor is uncertain and, in most cases, impossible to make, with the facilities available."

This resistance to surgical therapy is particularly prevalent with reference to patients in whom there are lesions referred to as circumscribed or round, whether they are symptomatic or asymptomatic. The term "round" or "circumscribed" unwittingly is a dangerous one because to many doctors a circumscribed or round lesion suggests only a benign tumor or cyst. The analogy with breast tumors is a fair one. It formerly was taught, and is still believed by many, that a circumscribed or round breast tumor was most likely to be a benign fibro-adenoma or cyst. Surgeons now agree that microscopic examination of frozen sections of a biopsy specimen is the only safe way to establish the differential diagnosis between benign and malignant breast lesions. The same holds true for chest tumors. It is most interesting to speculate on the nature of these lesions, but to be intellectually honest one must recognize that only the pathologist can establish the actual diagnosis after resection, excision, or biopsy. The prime duty of the physician, roentgenologist, and surgeon is to say to the patient: "There is a roentgenographic shadow that should not be present. The exact nature of it cannot be established without operation. I strongly urge you to have it removed at operation because of the possibility of malignancy."

Ten years ago the risk of exploratory thoracotomy may have justified hesitancy in removing an intrathoracic lesion which in more than 50 per cent of cases might prove benign. Today the risk of thoracotomy is virtually nil; the risk of lobectomy is less than 5 per cent and that of pneumonectomy is from 10 to 25 per cent. The risk is even less in asymptomatic patients.

The chest roentgenograms taken on induction into the Army and Navy and those taken by large industrial concerns have added considerably to our experience with "silent" lesions. Effler, Blades, and Marks (1) have recently described 24 cases of asymptomatic thoracic lesions discovered and operated upon in an Army hosptial during the war. These occurred in apparently healthy soldiers. O'Brien, Tuttle, and Ferkany (2) have also recently reported their experiences with 21 similar cases, referred to as pulmonary "coin" lesions because they were round (circumscribed). These also were discovered in apparently well individuals.

To illustrate the cases described in this paper, I have selected roentgenograms which present "silent" or "round" lesions and have indicated the preoperative pathologic diagnosis. These cases appear to illustrate clearly the gamut of pathology which must be considered in differential diagnosis.

SUMMARY

Intrathoracic lesions which are not causing symptoms and those which appear circumscribed on the roentgenogram of the chest are in more than half of the

cases ultimately shown to be malignant. Even those lesions which are benign in the usual sense of the word may not run a benign course. As a rule, the patient is best served by surgical removal of these unexplained and undiagnosed circumscribed lesions.

SUMARIO

Lesiones Asintomáticas del Tórax que Aparecen Circunscritas en la Radiografía

Las lesiones intratorácicas que no provocan síntomas y que parecen circunscritas en la radiografía resultan ser por fin malignas en más de la mitad de los casos. Hasta las que son benignas en el sentido habitual del vocablo tal vez no muestren una evolución benigna. Por regla general, el enfermo lo pasa mejor con la extirpación cruenta de esas inexplicadas lesiones circunscritas sin diagnóstico.

REFERENCES

(1) Effler, D. B., Blades, B., and Marks, E.: The problem of the solitary lung tumors, Surgery, 1948, *24*, 917.

(2) O'Brien, E. J., Tuttle, W. M., and Ferkaney, J. E.: The management of the pulmonary "coin" lesion, S. Clin. North America, 1948, *28*, 1313.

TUBERCULIN TESTING OF MIDSHIPMEN AND RECRUITS OF THE NAVY AND MARINE CORPS[1,2]

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INTRODUCTION

While our information concerning the exact mechanism of the tuberculin reaction must be regarded as incomplete, it is now generally agreed that natural hypersensivity to tuberculin is a result of tuberculous infection. In the clinical application of this fact, it is important to distinguish sharply between tuberculous infection and tuberculous disease. From tuberculin test surveys of our population and from examination of autopsy material, there is indication that the vast majority of tuberculous infections are promptly arrested and never produce tuberculous disease. Tuberculous infection, however, does leave its mark. The tissues of the host become sensitized to the products of the tubercle bacillus. This sensitization can be detected by the tuberculin skin test. The test, however, has limitations. A positive result does not indicate age of the infection, whether the infection is active, or whether the infection has progressed to disease. It merely indicates that the individual at some time in the past has been infected by the tubercle bacillus.

Since January 1942, fluorograms of the chest have been a part of the routine examination to determine physical fitness of inductees and applicants for the Navy and Marine Corps. In the spring of 1948 the tuberculin test was made a part of this routine. The advantages to be gained from the mass tuberculin survey of recruits are considered to be as follows:

1. The tuberculin test aids the roentgenologist and internist in deciding the significance of calcifications and infiltrates observed in the initial fluorograms.

2. The tuberculin test can be repeated in selected groups, particularly in those individuals exposed to tuberculosis, and close observation can then be made of those negative reactors whose reactions subsequently become positive.

3. A repeat tuberculin test found to be converted to positive and associated with a pulmonary infiltrate will serve, not only as an aid in diagnosis, but also as an aid in determining the age and hence the significance of the lesion.

4. The proportion of persons who have experienced a tuberculous infection prior to entering the service can be determined.

5. A recorded negative tuberculin test on enlistment will aid in establishing or disproving service connection to tuberculous disease discovered later. If it is found that a substantial number of the men who develop clinical tuberculosis

[1] Presented before the Medical and Public Health Sessions, as part of the symposium on *Modern Trends in Prevention and Treatment of Tuberculosis*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 25, 1950.

[2] The opinions and assertions contained herein are those of the authors and do not necessarily reflect those of the Navy Department or of the service at large.

incur their initial infection while on active duty, it will indicate the need for better control measures within the service. The question of BCG vaccination can then be discussed on firmer ground.

This report deals with the results of tuberculin testing of recruits received for training at one Marine Corps and two Naval Training centers during the last nine months of 1948. With few exceptions, all recruits were tested within four days after reporting for active duty from civilian life. The freshman class at the U. S. Naval Academy was also included in the testing.

Techniques and Procedures in Testing

The tuberculin used for testing was the Purified Protein Derivative, prepared in tablet form by Parke, Davis and Company. The tablets were of two sizes, one containing sufficient material for 50 tests and the other sufficient material for 250 tests. Measured amounts of sterile distilled water were provided in ampoules of the proper volume so that, if one tablet were dissolved in an ampoule, the resulting solution would contain 0.0001 mg. of tuberculin per 0.1 cc. The test was performed by injecting 0.1 cc. of the tuberculin solution intradermally into the volar surface of the forearm.

The test was interpreted after 48 to 72 hours. The result was recorded as negative if there was no edema at the site of injection even though redness was present. A doubtful reaction was one of slight redness and a trace of edema measuring 5 mm. or less in diameter. A positive test was one in which there was redness and a definite area of edema more than 5 mm. in diameter. The degree of reactivity, as determined by the diameter of induration, was recorded as follows:

1 + more than 0.5 cm., but not exceeding 1 cm.;
2 ++ more than 1 cm., but not exceeding 2 cm.;
3 +++ more than 2 cm.;
4 ++++ redness and edema plus an area of necrosis.

RESULTS OF TUBERCULIN TESTING

The results of tuberculin testing are shown in table 1. Of 79,393 tuberculin tests performed, 7,675, or 9.7 per cent, were positive. In table 2 the results are classified by the station of those tested. Although the difference in the percentage of reactors between any two of the four stations is small, there is a statistically significant difference between the percentage of reactors reported at the Naval Training Center, Great Lakes, and that reported at the Naval Training Center, San Diego.

In table 3 is shown the age distribution of the Navy and Marine Corps recruits enlisted during the calendar year 1948 and the midshipmen of the class tested. It will be noted that 72 per cent of the Navy recruits and 88 per cent of the Marine Corps recruits were in the age groups of 17, 18, and 19 years. The majority of the Navy recruits were 18 and 19 years of age. A correlation was made of the percentage of reactors in the various age groups for 10,000 Navy recruits. No significant difference was found in the percentage of reactors in any of the age groups reported.

It should be pointed out that Navy and Marine Corps recruits are not representative of the general population because of factors other than the restricted

age groups. For example, men with obvious physical defects, including tuberculosis, either do not apply for enlistment or are disqualified by physical examination at the recruiting station and do not reach the training center. The percentage of Negro recruits is less than 3 per cent, a figure somewhat lower than

TABLE 1

Results of Tuberculin Tests in Recruits and Midshipmen, Navy, and Marine Corps, 1948

Persons Tested, Classified by Reaction to 0.0001 mg. PPD Tuberculin

REACTION TO 0.0001 MG. PPD	PERSONS TESTED	
	Number	Per cent distribution
Total	79,393	100.0
Negative reaction	70,872	89.3
Doubtful reaction	844	1.1
Positive reaction	7,677	9.7
1 +	3,199	4.0
2 + +	2,470	3.1
3 + + +	1,541	1.9
4 + + + +	467	0.6

TABLE 2

Results of Tuberculin Tests in Recruits and Midshipmen, Classified by Station: Navy and Marine Corps, 1948*

STATION	NUMBER OF PERSONS TESTED	REACTIONS			
		Negative	Doubtful	Positive	Per cent positive
Total	79,393	70,872	844	7,675	9.7
Naval Training Center, Great Lakes, Illinois	45,625	41,126	388	4,111	9.0
Naval Training Center, San Diego, California	26,481	23,311	416	2,754	10.4
Marine Corps Recruit Depot, San Diego, California	6,469	5,740	32	697	10.8
U. S. Naval Academy (Class 1951), Annapolis, Maryland	818	695	8	115	14.1

* 0.0001 mg. PPD intradermally.

that found in the general population of the United States. Men with delinquent or criminal records are barred from enlistment. Since enlistments during 1948 were voluntary, the young men who wished to obtain a college education are not represented.

Comment on Significance of Reactions

Do the results of tuberculin testing as presented indicate that at least 90 per cent of the young men enlisting in the Navy and Marine Corps have not been infected with the

tubercle bacillus? This question certainly cannot be answered with an unqualified "yes" although there is fairly good support for an affirmative answer. In evaluating the tuberculin test, there are many factors which must be considered.

First are the factors which tend to bring about a false negative test. It is known that the degree of hypersensitivity or allergy wanes with years after an innocuous first infection, and eventually an individual may possess a degree of allergy so slight that it will not be detected by the ordinary doses of antigen used in testing. The age of the recruits here reported reduces the possibilities for the operation of this factor.

There are other conditions which depress tuberculin allergy, but fortunately these, such as fever, the exanthemas, and overwhelming tuberculous infection, are infrequent in occurrence and obvious when present.

There is good evidence to substantiate the statement that false positive reactions occur when the dosage of tuberculin is sufficiently great. Furcolow and his associates (1), in titra-

TABLE 3

Navy and Marine Recruits, 1948, and Midshipmen, Class of 1951 Classified by Age*

AGE	NAVY RECRUITS	MARINE RECRUITS†	MIDSHIPMEN
Total	100.0	100.0	100.0
17	13.8	28.1	0.0
18	33.7	37.2	14.0
19	25.0	22.5	35.3
20	9.9	7.2	37.7
21	4.2	2.0	8.2
22	4.1	1.2	3.3
23	3.2	0.6	1.2
24	1.8	0.4	0.1
25 or over	3.9	0.7	0.1

* From "Statistics of Military Personnel, Navy and Marine Corps" 1948.

† Marine recruits enlisted July–December 1948.

tion studies of tuberculin, found that a dose of 0.0001 mg. PPD (the same as used in the study here reported) was sufficient to provoke a reaction of five or more millimeters of induration almost uniformly in those individuals tested having known tuberculosis and in a high proportion of those giving a history of contact with tuberculosis. This dosage, however, produced relatively few reactions among children considered free of the disease and without known exposure.

When the dose of tuberculin was successively increased, almost all of the individuals tested eventually reacted to the antigen, including infants and young children without evidence of tuberculous infection or history of contact. It is improbable that such a high proportion of children were actually infected with tuberculosis. The explanation advanced by the authors is that, with the use of higher doses of the antigen, nonspecific reactions appear with increasing frequency. Palmer (2) states that infections with other acid-fast bacilli, nonpathogenic for man, may result in a state of hypersensitivity which is detectable by tuberculin when high doses are used in testing.

The first and second strengths of PPD tuberculin are commonly employed in this country in performing the intradermal (Mantoux) test. The second strength (0.005 mg.

per dose) is 250 times as strong as the first strength (0.00002 mg. per dose) and 50 times as strong as the intermediate strength (0.0001 mg. per dose) used in the mass survey of Navy and Marine recruits.

TABLE 4

Persons Tested Who Were Found Negative to 0.0001 mg. PPD, Classified by Reaction to 0.005 mg. PPD

REACTION TO 0.005 MG. PPD	PERSONS TESTED WHO WERE FOUND NEGATIVE TO 0.0001 MG. PPD	
	Number	Per cent distribution
Total	450	100.00
Negative	152	33.8
Doubtful	15	3.3
Positive	283	62.9
1 +	139	30.9
2 + +	96	21.3
3 + + +	48	10.7
4 + + + +	—	—

TABLE 5

Persons Tested Whose Reactions to 0.0001 mg. PPD were Doubtful, Classified by Reaction to 0.005 mg. PPD

REACTION TO 0.005 MG. PPD	PERSONS TESTED WHOSE REACTIONS TO 0.0001 MG. PPD WERE DOUBTFUL	
	Number	Per cent distribution
Total	50	100.0
Negative	—	—
Doubtful	—	—
Positive	50	100.0
1 +	—	—
2 + +	11	22.0
3 + + +	39	78.0
4 + + + +	—	—

It was decided to retest a sample of the nonreactors and a sample of the doubtful reactors, using the second-strength tuberculin.[3] The samples were picked at random and without knowledge of the roentgenographic findings. As shown in table 4, 63 per cent of a group of 450 nonreactors to the 0.0001 mg. dose exhibited positive reactions when retested with the 0.005 mg. dose. Fifty doubtful reactors to the 0.0001 mg. dose were retested with the 0.005 mg. dose, and all showed positive reactions with more than 1 cm. of induration (table 5). In the groups retested, no reaction was severe enough to produce necrosis of the skin. Photo-

[3] PPD-S supplied by Field Studies Branch, Division of Tuberculosis, Public Health Service.

roentgenographic survey of the entire group of recruits and midshipmen here reported disclosed pulmonary infiltrates in approximately one per 1,000 men examined. It appears most unlikely that 66 per cent of the group of 500 recruits retested had experienced tuberculous infection.

Edwards, Lewis, and Palmer (3), studying student nurses, found that the frequency of pulmonary infiltrates was constantly very low among individuals showing less than 0.5 cm. of definite induration to the 0.0001 mg. dose of tuberculin, regardless of the degree of hypersensitivity shown to the 0.005 mg. dose. It was found, however, that in nurses who demonstrated 0.5 cm. or more of definite induration to the 0.0001 mg. dose there was a greater frequency of infiltration.

These studies suggest that, in young adults, a dosage of PPD tuberculin of approximately 0.0001 mg. will produce positive reactions in the greatest proportion of individuals who have experienced infections with the tubercle bacillus and negative reactions in the greatest proportion of those who have not experienced such infections. A plea is made to those who report the results of tuberculin skin tests, either in clinical records or in publications, to state the *type* and *dosage* of the antigen used.

SUMMARY

1. The results of intradermal tuberculin skin testing of midshipmen and Navy and Marine recruits and a discussion of the significance of the tuberculin test are presented.

2. Of 79,393 men tested, 9.7 per cent showed positive reactions to a dose of 0.0001 mg. PPD tuberculin. In Navy recruits, the proportion of reactors was slightly higher (10.4 per cent) in men who enlisted in the southern and western states than the proportion (9.0 per cent) for men who enlisted in the north central and northeastern states.

3. Approximately 84 per cent of the recruits and midshipmen reporting for training during 1948 were of the age group of 17 through 20 years. Caution should be used in applying these results even to the same restricted age groups of the general population because of certain factors which influence the selection of midshipmen and recruits for the service.

4. The second strength of PPD tuberculin (0.005 mg. per dose) produced a high proportion of presumably nonspecific reactions in a group of 500 Navy recruits retested.

Acknowledgments

Grateful acknowledgment is made to the medical department personnel of each training activity here reported. These personnel did the work. Special recognition is given Captain T. J. Carter (MC), USN, and his staff at the Naval Training Center, San Diego, who performed and interpreted the 500 repeat tuberculin tests.

REFERENCES

(1) Furcolow, M. L., Hewell, B., Nelson, W. E., and Palmer, C. E.: Quantitative studies of tuberculin reaction: Titration of tuberculin sensitivity and its relation to tuberculous infection, Pub. Health Rep., 1941, *56*, 1082.

(2) PALMER, C. E., AND PETERSEN, O. S.: Studies of pulmonary findings and antigen sensitivity among student nurses: V. Doubtful reactions to tuberculin and to histoplasmin, Pub. Health Rep., 1950, *65*, 1.

(3) EDWARDS, L. B., LEWIS, I., AND PALMER, C. E.: Studies of pulmonary findings and antigen sensitivity among student nurses: III. Pulmonary infiltrates and mediastinal adenopathy observed among student nurses at the beginning of training, Pub. Health Rep., 1948, *63*, 1569.

THE EFFECT OF ANTIHISTAMINICS ON THE TUBERCULIN SKIN REACTION[1,2]

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INTRODUCTION

The role of hypersensitivity in tuberculosis has been studied and discussed at considerable length since 1890. In that year, Koch published the first of his papers (1, 2) in which he discussed his "remedy for tuberculosis (tuberculin)" and described the local result of reinfection, known since as the Koch phenomenon. The role of hypersensitivity in tuberculosis is still incompletely explained. Despite many differences between the tuberculin or cellular type of hypersensitivity and humoral hypersensitivity (3), there are many similarities. The success of antihistaminics in allergic disorders has stimulated the trial of antihistaminics in tuberculosis. During the past year several reports pertaining to the use of antihistaminics in tuberculosis have appeared (4, 5, 6, 7).

Criep, Levine, and Aaron (4) found no influence on the Mantoux test resulting from large oral doses (400 mg. daily) of Pyribenzamine. They also found little effect on either the patch or intradermal tuberculin test when these were applied at sites previously infiltrated by injection or by iontophoresis with Pyribenzamine. They concluded: "The tuberculin type of sensitivity reaction is not affected by antihistaminic drugs. . . ."

Judd and Henderson (5) reported 30 cases in which clinical improvement, especially in tuberculous pneumonia and other exudative lesions, apparently followed the administration of antihistaminics. These workers noted that "in most instances a gradual diminution in the intensity of the reactions occurred while antihistaminic drugs were taken." They concluded ". . . it would appear from our results that clinical improvement roughly parallels suppression of the Mantoux reaction." Friedman and Silverman (6) studied a group of children with an initial tuberculin test and with a second test read after four days of Pyribenzamine administration. They noted no effect on the tuberculin skin reaction from Pyribenzamine in doses of 60 mg. or 240 mg. daily. Henderson (7) in a letter to the editors of THE AMERICAN REVIEW OF TUBERCULOSIS commented on the report of Friedman and Silverman and stated, "When 500 milligrams of drug are given for six months with pulmonary and other forms of tuberculosis, one begins to see the results that cannot possibly be seen by employing 60 milligrams for four days."

[1] From the Pulmonary Disease Service, Birmingham Veterans Administration Hospital, Van Nuys, California.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE 1

Weekly Tuberculin Skin Tests of All Patients Studied

PATIENT		WEEKS OF TEST						
		1	2	3	4	5	6	7
		No Medication			Pyribenzamine			
G. A.	E	12	8	19	13	22	12	33
	I	12	8	18	12	22	12	33
D. B.	E	13	11	13	18	13	14	12
	I	13	11	13	14	15	14	12
G. B.	E	12	41	15	27	13	—	12
	I	12	13	15	16	13	—	12
G. B.	E	18	13	10	12	12	12	16
	I	18	13	10	12	12	12	16
R. C.	E	14	13	18	19	20	17	15
	I	14	13	18	19	20	17	15
J. C.	E	45	40	16	24	13	12	11
	I	10	12	16	15	13	12	11
		No Medication			Pyribenzamine		Benadryl	
D. F.	E	14	14	20	7	13	18	13
	I	14	13	20	7	13	18	13
J. F.	E	12	16	37	15	26	16	15
	I	12	16	19	12	18	16	15
J. F.	E	20	24	20	20	35	6	12
	I	10	15	20	15	35	6	12
M. F.	E	25	30	33	16	12	26	41
	I	25	29	33	16	12	26	25
L. G.	E	30	—	27	23	15	16	14
	I	15	—	15	21	15	16	14
T. H.	E	30	47	42	15	50	35	33
	I	30	30	20	13	17	35	33
J. J.	E	10	9	7	8	—	11	8
	I	10	9	7	8	—	11	8
W. K.	E	50	55	75	54	21	—	—
	I	15	18	75	22	21	—	—
J. L.	E	12	4	15	—	14	12	8
	I	12	4	15	—	14	12	8
J. M.	E	13	13	12	15	10	18	12
	I	8	13	12	12	10	18	12
J. M.	E	12	9	14	8	10	8	10
	I	8	9	14	7	8	8	10
L. M.	E	41	55	50	21	41	13	23
	I	18	15	18	20	41	13	23
T. S.	E	17	11	20	12	12	10	9
	I	17	11	20	10	12	10	9
E. S.	E	10	13	10	18	10	16	18
	I	10	13	10	12	7	16	18
J. T.	E	32	37	33	47	10	28	21
	I	16	20	33	30	10	28	21
J. T.	E	28	22	31	26	25	24	30
	I	28	22	31	26	25	24	30

TABLE 1—*Continued*

PATIENT		WEEKS OF TEST						
		1	2	3	4	5	6	7
		No Medication (Controls)						
J. H.	E	6	15	23	15	14	13	11
	I	6	15	23	15	14	13	11
T. R.	E	16	13	10	12	16	15	24
	I	16	13	10	12	16	15	24
A. S.	E	16	60	7	22	13	16	14
	I	16	23	7	22	13	16	14
A. R.	E	9	12	22	20	18		
	I	9	12	22	20	18		
S. N.	E	6	8	11	11	13		
	I	6	8	11	11	13		
J. A.	E	30	24	22	23	10		
	I	20	20	22	18	10		
R. O.	E	30	23	21	23			
	I	19	22	21	23			
A. C.	E	16	22	21	19			
	I	13	20	21	19			
A. L.	E	13	—	45	18	19		
	I	13	—	22	18	19		
H. G.	E	10	28	26				
	I	10	28	26				
A. M.	E	35	40	34				
	I	22	35	34				
		No Medication				Benadryl		
Z. M.	E	15	95	50	55	25	41	—
	I	12	70	50	22	18	41	—

The present study is an attempt to evaluate the effect of usual doses of antihistaminics on the tuberculin skin reaction.

Methods of Study

Twenty-three hospital patients with minimal to far advanced pulmonary tuberculosis, lymph node tuberculosis, renal tuberculosis, or tuberculous pleural effusion, who had positive skin tests to first-strength purified protein derivative tuberculin, were tested throughout a seven-week period. Tuberculin skin tests were done at weekly intervals by injecting 0.1 cc. of PPD no. 1 tuberculin (0.00002 mg.) intradermally and reading the skin reactions forty-eight hours later. All injections were made by two physicians and all of the tuberculin reactions were measured by one of these physicians. The diameter of induration and erythema was recorded for each reaction.

During the first three weeks, no antihistaminic medications were given and weekly Mantoux tests were performed. After the third test was read, all of the 23 patients were given Pyribenzamine in a dosage of 50 mg. four times daily. One patient showed intolerance within twenty-four hours and Pyribenzamine was changed to Benadryl, 50 mg. four times daily, which he tolerated fairly well and took for four weeks. Six patients received Pyribenzamine for four weeks. Sixteen patients received Pyribenzamine for two weeks, and

15 of these received Benadryl for the following two weeks. (The sixteenth man was discharged after two weeks of Pyribenzamine administration.) Thus, antihistaminics had been given for seven days at the time the fourth tuberculin test was read, and for twenty-eight days when the seventh tuberculin test was read.

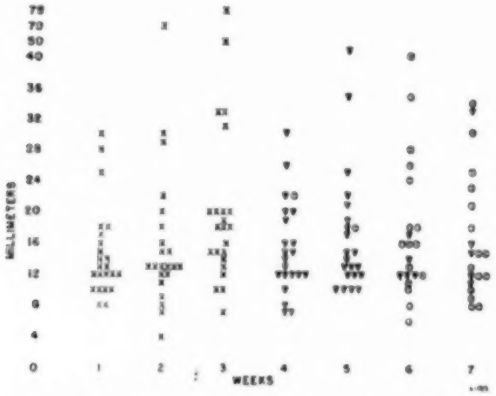

FIG. 1. Diameter of tuberculin reaction induration during: × Control period of no medication, ▽ Pyribenzamine administration, ○ Benadryl administration.

FIG. 2. Diameter of tuberculin reaction induration during: × No medication.

The 28-day course of Pyribenzamine was given to 6 patients to determine whether this longer course of one antihistaminic would produce any different results. These patients were the first 6 in the alphabetical list of the 23. Their tuberculin reactions were similar to those in the previous groups.

Another group of 11 patients with tuberculosis on an adjacent ward were used as controls and were given weekly tuberculin tests for three to seven weeks. No antihistaminics were given.

RESULTS

In table 1 are recorded the measurements of both erythema and induration in all of the tests performed. It is realized that only induration is of importance in the practical reading of tuberculin skin test response. The diameter of erythema

FIG. 3. Diameter of tuberculin reaction induration during: × No medication, ▽ Pyribenzamine administration.

TABLE 2

Tuberculin Skin Reaction

Median Diameter (mm.) of Induration Classified by Period

PERIOD	MEDIAN DIAMETER IN MILLIMETERS OF INDURATION			CONTROL GROUP (11 PATIENTS)
	Treated Group (23 patients)			
	During period without medication	During administration of Pyribenzamine	During administration of Benadryl	
All periods	14.5	14	16	16
1 week	13			14
2 weeks	13			21
3 weeks	18			22
4 weeks		14	*	18
5 weeks		14	*	14
6 weeks		12	16	15
7 weeks		15	15	14

* Insufficient data.

bore no consistent relationship to the diameter of induration, and showed wide variations in both study and control groups. Therefore, only induration is recorded in the subsequent text and figures. Serial tuberculin skin reactions varied whether or not antihistaminic medications were being administered. Marked variations in intensity of positive reactions were observed in successive weeks.

It would seem, therefore, that the value of the tuberculin test lies solely in its negativity or positivity, and not in variations of positivity.

A scattergram (figure 1) records all tuberculin tests performed on the study group. The distribution shows no change during Pyribenzamine or Benadryl administration. Tests performed on the control group are similarly diagramed in figure 2. The distribution is comparable with that of the group treated with antihistaminics. The tuberculin test responses of the 6 men who received four weeks of Pyribenzamine are illustrated in figure 3. Throughout the seven-week period there appeared to be no change in the tuberculin reaction greater than that seen in control patients.

Further analysis of these data is presented in table 2. As may be seen, the same differences in the median diameter of induration from week to week in the treated group were observed both before and during administration of antihistaminic drugs. Moreover, differences of equal magnitude were apparent in the control group.

From the data presented, it may be concluded that in the dosage administered in this study these drugs have no effect on the tuberculin skin reaction.

SUMMARY

Two representative antihistaminic drugs administered in the usual clinical dosages (200 mg. daily) for four weeks had no effect on the tuberculin skin reaction. Moreover, there was no demonstrable effect of these drugs on the course of the tuberculosis of the patients in this study.

The marked variations observed in the diameter of the area of induration and the even more marked variations in the diameter of erythema make it apparent that no significance can be attached to the actual intensity of the reaction in a given case. It is probable that any palpable area of induration should be reported simply as a positive test, although it has been a frequent practice to consider only areas 5 mm. in diameter or greater as positive reactions.

SUMARIO

El Efecto de los Antihistamínicos sobre la Cutirreacción a la Tuberculina

Dos típicos antihistamínicos administrados a las habituales dosis clínicas (200 mg. diarios) durante cuatro semanas no ejercieron efecto alguno sobre la cutirreacción a la tuberculina. Además, tampoco hubo en este estudio efecto demostrable de dichas drogas sobre la tuberculosis de los enfermos.

Las notables variaciones observadas en el diámetro de la zona de induración y las variaciones aun más notables en el diámetro del eritema ponen de manifiesto que no cabe conceder importancia alguna a la intensidad de la reacción en un caso dado. Es probable que toda zona palpable de induración debe ser registrada meramente como reacción positiva, aunque frecuentemente hasta ahora se han considerado como positivas únicamente las zonas de 5 mm. o más de diámetro.

REFERENCES

(1) Koch, R.: Weitere mittheilungen uber ein heilmittel gegen tuberkulose, Deutsch. med. Wchnschr., 1890, *16*, 1029.

(2) Koch, R.: Fortsetzung der mittheilung uber ein heilmittel gegen tuberkulose, Deutsch. med. Wchnschr., 1891, *17*, 101, 1189.
(3) Pinner, M.: Pulmonary Tuberculosis in the Adult, Charles C Thomas, Springfield, Illinois, 1947, 113.
(4) Crief, L. H., Levine, M. I., and Aaron, T. H.: Inhibition of the tuberculin-type reaction by antihistaminic drugs and rutin, Am. Rev. Tubere., 1949, *59*, 701.
(5) Judd, A. R., and Henderson, A. R.: The use of antihistaminic drugs in human tuberculosis: A preliminary report, Ann. Allergy, 1949, *7*, 306.
(6) Friedman, E., and Silverman, I.: The effect of antihistamine medication on the tuberculin reaction in children, Am. Rev. Tubere., 1949, *60*, 354.
(7) Henderson, A. R.: The effect of antihistamine medication on the tuberculin reaction (letter to the editors), Am. Rev. Tubere., 1949, *60*, 811.

THE MENTAL ASPECTS OF TUBERCULOSIS[1]

Observations Based on a Veterans Hospital Study[2]

GEORGE E. DANIELS AND EUGENE DAVIDOFF

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INTRODUCTION

An increasing number of diseases which constitute the chief causes of death and disability are being studied for evidence of emotional factors either as contributing to the etiology or as important complications of the disease. Coronary artery disease, hypertension, diabetes, asthma, and a host of other diseases are being so scrutinized. Pulmonary tuberculosis is one of the latest to come under systematic psychiatric study. With tuberculosis, as with the other conditions mentioned, a mass of generalizations concerning the personality reactions has been accumulated during the years— the precipitate of superstitions and impressions that must be reassayed for the facts. Some of these impressions are that tuberculous patients are likely to be overly optimistic and euphoric, especially in the terminal stages; that tuberculosis is often associated with genius and tends to promote it; and that the disease stimulates sexual activity (1).

A more recent impression seen in the literature is that severe, chronic emotional conflict, shattering reverses, or responsibilities beyond the individual's tolerance may be factors in initiating tuberculous infection or in bringing about a reactivation of an old lesion. For example, in a study of 75 patients, Strecker, Braceland, and Gordon (2) report that a number of patients were sure that various marital, physical, and economic stresses were the cause of their disease; and that a few patients were being treated for nervous breakdowns when tuberculosis was detected. Many so-called nervous breakdowns, which on the surface appear to be caused by overwork, reveal under psychiatric review situations of conflict which have furnished the impetus toward the activity that proved to be so exhausting. In how many cases of tuberculosis may these same factors lead to exhaustion and reduced resistance, thus increasing the susceptibility of the individual to infection?

Wittkower and Todd (3), in an extremely thoughtful article, state that more often than is generally known severe emotional conflicts precede the onset of illness and assume the appearance of a precipitating factor. Most of us who have had experience with sanatorium patients can recall hearing such stories. Although the validity of such an impression must await further and more precise study, if this impression does prove valid in tuberculosis, as in other organic diseases in which a definite emotional component has been demonstrated, mental hygiene will be an important part of prevention and treatment.

[1] Presented before the Medical and Public Health Session, as part of the symposium on *Modern Trends in Prevention and Treatment of Tuberculosis*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 25, 1950.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Whether or not conflict contributes to the outbreak of the disease, we cannot but recognize that treatment, as presently organized, furnishes an ideal escape from the vicissitudes of life. Taking to one's bed is known to be a convenient protection from the assaults of a hostile environment. As Wittkower and Todd (3) point out, for some patients who may have been under severe emotional stress admission to a sanatorium constitutes a temporary, although usually unsatisfactory, resolution of their emotional problems which generally will have to be met again on discharge. Whether or not the patient comes to the sanatorium with emotional problems, the present regimen of strict bed rest and relief from all possible responsibilities promotes a period of passivity and dependence for those who obey the rules and a situation of disapproval of, and conflict with, authority for those who do not. Too complete an acquiescence to treatment, although beneficial for the physical condition, may for some individuals become crippling to the personality. Under all circumstances it has been found that a fairly gradual return to activity and responsibility is necessary. With a chronic disease like tuberculosis, in which treatment is likely to be measured in units of six months or a year, any aids which can promote recovery and prevent unnecessary delay in rehabilitation would be welcome. The present report summarizes observations on the mental aspects of tuberculosis made by a psychiatric team in a pilot study conducted in a Veterans hospital.

Outline of Study

The study that is the basis of this communication was undertaken in 1947–1948 by the Veterans Administration at the suggestion of Dr. Carl Binger and with the approval of Dr. Daniel Blain, then Chief of the Psychiatric Division, and with the enthusiastic participation of Dr. John Barnwell, Chief of the Tuberculosis Section. A committee of consultants in psychiatry and tuberculosis[2] developed a plan for a pilot study to be undertaken at Sunmount Veterans Hospital, a 570-bed institution in the village of Tupper Lake, New York, in the Adirondacks. Among the considerations leading to this choice was our assurance of the enthusiastic support of the manager, Dr. Henry Walters, and the definite emphasis on investigation as well as treatment, which has been a part of the atmosphere of this hospital in recent years. The project was also aided by the active cooperation of Dr. N. D. D'Esopo, Chief of the Medical Service at Sunmount, who took part in the initial planning and with his staff[4] ensured complete medical coverage and integration of psychiatric team activities with the medical program.

Although sporadic psychiatric studies have been made of tuberculous patients in institutions, so far as we know they have never been undertaken with the complete psychological coverage which this study represents. The Sunmount Plan called for the residence at the hospital of a psychiatric team made up of a chief psychiatrist, an assistant psychiatrist, a psychologist, a social worker, and a psychiatric nurse.[5] The team's function was not

[2] The committee consisted of Dr. Carl Binger, chairman; consultants for tuberculosis: Dr. Jonn Barnwell, Dr. J. Burns Amberson, Dr. Cameron St. C. Guild, Dr. Gilberto S. Pesquera, and Dr. James W. Waring; consultants for psychiatry: Dr. Daniel Blain, Dr. Carl Binger, Dr. Irwin Cohen, Dr. George E. Daniels, Dr. Nils B. Hersloff, Dr. Howard W. Potter, and Dr. Harvey Tompkins.

[4] Medical staff: Dr. Nicholas D. D'Esopo, Dr. James W. Raleigh, and Dr. John Steinhaus.

[5] Dr. Eugene Davidoff, psychiatrist-in-chief; Dr. Harold Wolman, psychiatrist; Mr. Howard Mausner, psychologist; Mrs. Anne B. Hunt, psychiatric nurse; Mrs. Mary Reichsman, social worker.

only to accumulate information and explore existing personality problems in tuberculosis, but to act as an active resident unit during its stay, with the purpose of perfecting such units for eventual application in other tuberculosis hospitals, Veteran and non-Veteran.

Twenty patients who had been in the hospital at least three months were selected for study. The three-month period gave the patients time to effect their particular adjustment to hospitalization and to afford the hospital staff an opportunity to observe their behavior and to compile at least a minimum amount of medical and laboratory data. In order to explore the existing medical criteria for adjustment to the hospital and to combine this information with the psychiatric evaluation of adjustment to the hospital and to their disease, the medical staff was asked to pick 10 patients whom they considered well adjusted to the hospital and 10 who were considered poorly adjusted.

There were frequent conferences and good liaison with the medical service, as well as active cooperation with the hospital personnel generally. This coordination was not only essential for obtaining a complete medical and psychiatric picture of the patients studied, but it also gave maximum impact and diffusion of psychiatric education for both patients and staff.

In addition to psychiatric observation, including examination and history taking, there were follow-up interviews, the frequency depending on the case. A complete social service history was taken by the team social worker, who also attended to the practical details of the case, working with the hospital social service department when feasible. Without previous consulting of the patients' records, the psychologist administered a battery of tests, including the Rorschach, as a check on the clinical findings. The psychiatric nurse had access to information already available in past records kept by the regular nursing service. Her hours on duty as a floor nurse were integrated with the regular schedule and were arranged to afford sample nursing coverage of the 20 patients during their entire twenty-four-hour day. Regular and frequent conferences were held by members of the psychiatric team to coordinate and crystallize their impressions of the patients under study.

OBSERVATIONS

Depression in tuberculosis: We will not discuss the question of the relation of pulmonary tuberculosis to genius and increased sexual activity. These concepts, however, like the association of tuberculosis with a predominating euphoric, overly optimistic reaction, are proving to be unwarranted textbook generalizations. The question of the prevailing or most frequent mood became a matter of our special interest. Our own findings, as well as those of other investigators, show that depression is actually the most frequent. Depression appeared clearly in 9 of the 20 patients, and there were traces of this reaction at some time in most of the patients. Strecker, Braceland, and Gordon (2) list depression as the predominating reaction in 29 of their 75 patients, whereas only 7 were characterized as questionably happy and another 4 described as experiencing marked swings of mood in both directions.

Wittkower and Todd (3) report that most patients with pulmonary tuberculosis are in a mood of mildly overt or concealed depression and anxiety which they consider, on the whole, to be explained by the limitations and burdens imposed by a debilitating chronic disease like tuberculosis. They point out that defiance and ultra-cheerfulness are also encountered and are liable to represent

the bold front that patients put up to hide their deeper depression and misgivings. Strecker, Braceland, and Gordon (2) describe how this spurious cheerfulness may be assumed by patients during medical ward rounds made by the chief of service and his staff, only to be dropped immediately after. When the psychiatrist returned promptly to the same ward, the picture had changed and the more habitual dejection had again assumed its predominant role. One cannot help wondering to what degree the false generalizations regarding prevailing optimism in patients with pulmonary tuberculosis may have originated from such uncritical official observations.

Our own psychiatric team found that mild swings in mood represented a common tendency, with depressive reactions predominating. Later reconstruction of the premorbid personality from the history gave the impression that such a tendency toward swings in mood was the most general personality trait encountered in the group. This tendency had been evoked by other crises in addition to the tuberculosis, both in civilian and military life. These reactions might be best referred to as subclinical since the past histories revealed that the prevalence of generally accepted psychiatric categories among the 20 patients was not remarkable. One patient among those with a history of mood swings was psychotic; and 3 patients were diagnosed as schizoid personalities. None could be diagnosed as either schizophrenic or suffering from definite manic depressive insanity. Two showed evidence of long-standing psychoneuroses, and 2 patients had a history of antisocial aggressive reaction on the border of psychopathic personality.

Importance of psychosomatic history: In cases of tuberculosis, as in all organic conditions that have emotional components, a good psychosomatic history is essential. This is a necessary starting point for investigation or psychotherapy; when the material is gathered skillfully, such history-taking in itself may have a therapeutic effect.

The taking of a psychiatric history designed to reveal psychosomatic problems has been covered well in other communications (4, 5). One of the most essential parts of such a psychosomatic history is a good account of the family environment, childhood, and school and marital status. These items are often classified under the more general heading of personal history. Such a personal history can be very elaborate or very simple, depending on the experience and training of the physician, as well as on the time at his disposal. At least a simple personal history should be taken in cases of pulmonary tuberculosis. Much of this data often remains buried in the social service history. A few routine questions about conditions of his work, general development, and family life will often reveal essential psychosomatic data when such direct questions as, "Are you nervous?" or "Do you have any serious troubles or worries?" bring a denial, perhaps because the patient shrinks from such admissions or because he himself is not sufficiently conscious of conflicts to give a direct answer.

Although the team program called for emphasis on investigation and no extensive psychotherapy was attempted, the process of history-taking and interviewing in the personality field had a psychotherapeutic effect in certain cases.

In addition to this general beneficial effect, the team member handling a patient had in mind implications of treatment and utilized the opportunity to carry these out when possible. It has been repeatedly demonstrated with groups of various kinds that, by expressing complaints and dissatisfactions, not only have the individuals themselves often been relieved through the expression of their resentment, but the general morale of the groups is improved (6). Dissatisfactions with progress of treatment, with conditions at home, or with conditions in general, are often expressed through criticism of the hospital personnel, the treatment regimen, and particularly of food, the most convenient whipping boy. Although such "grousing" may represent a necessary safety valve if a better therapeutic outlet is not at hand, such complaints are liable to be diffused generally and impair general morale. The psychiatric unit did not remain at Sunmount long enough to measure the general effects of its presence, but the definite impression was gained that some of this type of group therapy was set in operation.

An attempt was made by the psychiatrists and team personnel to guide the aggression and hostility into more constructive channels, such as planning and working for the future, use of the educational and rehabilitation program, and so on. In some patients, expression of anxiety over increase in activity gave opportunity for the team member to give reassurance and stimulation toward activity that they were considered physically able to tolerate. No attempt at prolonged psychotherapy was made, but recommendations were made concerning patients for whom such therapy was indicated. Research into the effect of intensive psychotherapy in selected cases is on the agenda for the next project.

Our experience indicated that, in general, the personality reactions manifested in the hospital reflected the previous personalities of the patients. If revolt against authority was characteristic of the patient's attitude toward his parents or those in a corresponding position of authority in civilian and military life, one could be reasonably sure that there would be evidence of insubordination in relation to hospital discipline.

Analysis of the "good" patient: Of the 10 patients designated as poorly adjusted by the medical staff, 6 absented themselves without leave and were discharged against medical advice. They were restless, unstable individuals. Of the 4 remaining patients, 2 were discharged prematurely, but on follow-up were found to have made a good adjustment on the outside. One other patient finally adjusted well and was discharged to attend a university. Still another veteran was in the hospital at the time the report was made, one year and a half after the study was begun.

Of the 10 patients who were considered well adjusted by the hospital staff, none absented themselves without leave. Five of these men, however, were still in the hospital at the end of the year and a half, and the course of their disease appeared to have been prolonged.

Apparently the original criterion for adjustment was based largely on how well the patient submitted to hospital discipline. It was worthy of note that, since

8 of the 10 so-called well-adjusted patients retained the active phase of the disease for a long time, the reaction to their illness could not be considered as satisfactory as their adjustment to the hospital. This conclusion led to an important consideration, namely, that the so-called "good" patient who yields, is submissive, and does not verbalize his complaints may be considered well adjusted to prolonged hospital stay because of a deep-seated desire to remain in the hospital and not face the outside world. Such a patient is often more in need of psychotherapy than the aggressive, restless individual who tells the clinician just how he feels and what he thinks and has a driving desire to get well and go home.

With the generally increased sophistication regarding psychosomatic conditions both within the profession and among the laity, one warning needs to be sounded. If a patient seems to be enjoying his invalidism or lags behind in his application to new recommended activities, it is both unscientific and damaging to consider him a malingerer unless this is found to be so in the narrower sense of the word. Some of the causes of prolonged invalidism may be quite evident to the disinterested onlooker, but almost completely obscured from the patient because of emotional blocks. Perhaps it is a bad situation outside to which the patient hesitates to return. Months of training in passive acceptance of treatment may have undermined his initiative and ability to accept responsibility, and this initiative may have to be gradually rebuilt. Last of all, he may have had an incipient neurosis before entering the hospital, and he may be utilizing the illness as a neurotic solution. The patient's own doctor may recognize the factors that tend to prolong his illness, or it may take a psychiatrist to unearth them. Whatever the situation, it should be considered as one of the medicosociologic problems to be solved, and not as a sign of his weakness with which periodically and harshly to face the patient. The latter action may drive him further into his invalidism instead of having the desired effect of relieving him of it.

SUMMARY

The Sunmount study herein reported was undertaken as a pilot study of the mental aspects of pulmonary tuberculosis in 20 patients in a Veterans Hospital population. It demonstrated the usefulness of a thorough personality study of patients in planning more comprehensive treatment. It indicated that behavior in the hospital was consistent with earlier behavior patterns in the life history of the individual, and that knowledge of the patient's personal history is, therefore, useful for prognosis, practical management, and psychotherapy. It was also the conclusion of the team that too much could not be expected of the tuberculosis specialist in the cure, either physical or mental, of patients with the following personality patterns: the patient who is psychotic or borderline, the antisocial individual or the person who has engaged in a lifelong history of misconduct, the excessively alcoholic, the hypomanic or severely depressive, the mentally defective, and the excessively neurotic. The Veterans Administration is planning to report this experience in more detail in a forthcoming monograph and to continue the much-needed research in this field.

SUMARIO

Los Aspectos Mentales de la Tuberculosis

Observaciones Basadas en un Estudio en un Hospital de Veteranos

El Estudio en Sunmount, aquí discutido sucintamente, fué emprendido como investigación orientadora o guía de las fases mentales de la tuberculosis pulmonar en 20 enfermos de un hospital para veteranos del Ejército de E. U. A. Demostró, entre otras cosas, la utilidad que reviste el estudio detenido de la personalidad de los pacientes cuando se trata de formular un tratamiento más amplio. Indicó que el comportamiento en el hospital armonizaba con anteriores formas de conducta en la historia del individuo y que, por consiguiente, el conocimiento de los antecedentes personales del enfermo resulta útil para el pronóstico, la asistencia práctica y la psicoterapia. Otra conclusión del grupo de estudio fué que no cabe esperar demasiado, de parte del tisiólogo, en la curación de los enfermos que muestran los siguientes patrones de personalidad: sujetos psicóticos o parapsicóticos, individuos antisociales, o personas con historia de mala conducta toda su vida, hiperalcohólicos, hipomaníacos o intensamente deprimidos, defectuosos mentales e hiperneuróticos. La Administración de Veteranos abriga el proyecto de publicar este estudio con mayor pormenor en una monografía y continuar las investigaciones, tan necesarias, de este tema.

REFERENCES

(1) Berle, B. B.: Emotional factors and tuberculosis: A critical review of the literature, Psychosom. Med., November–December 1948, *6*, 366.

(2) Strecker, E. A., Braceland, E. J., and Gordon, B.: Mental attitudes of tuberculous patients, Ment. Hyg., 1938, *22*, 529.

(3) Wittkower, E., and Todd, G. S.: The psychological aspects of sanatorium management, Lancet, 1948, *1*, 49.

(4) Daniels, G. E.: The psychosomatic approach in medical practice, Bull. New York Acad. Med., second series, 1948, *4*, 209.

(5) Weiss, E., and English, O. S.: Psychosomatic Medicine; The Clinical Application of Psychopathology to General Medical Problems, ed. 2, Philadelphia, W. B. Saunders Co., 1949.

(6) Roethlisberger, F. J., and Dickson, W. J.: Management and the Worker; An Account of a Research Program Conducted by the Western Electric Company, Hawthorne Works, Chicago; with the assistance and collaboration of Harold A. Wright, Cambridge, Massachusetts, Harvard University Press, 1939.

THE INFLUENCE OF EXTERNAL FACTORS ON PULMONARY TUBERCULOSIS[1, 2]

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INTRODUCTION

It is the purpose of this paper to set forth certain of the events which are related, temporally or otherwise, to unexpected changes in the course of patients with tuberculosis and which too frequently are overlooked as factors in the causation of the change.

When a patient with tuberculosis is started on an effective regimen of treatment and makes satisfactory progress, it is all too common that the disease grows worse despite adherence to the treatment regimen. When the patient leaves the hospital, his disease arrested, and follows conscientiously the plan recommended by his physician, it is not uncommon that the reactivation of the disease ensues. Lacking specific information on most of the many possible factors involved, one feels that these exacerbations and remissions in the cause of chronic pulmonary tuberculosis must be related to fluctuations in the patient's resistance. Certain factors are widely believed to be of importance in relation to resistance to tuberculosis. Outstanding among these is the effect of malnutrition on tuberculosis.

The experience of blockaded countries in World War I and that of the concentration camps in World War II show clearly the effects of poor nutrition on the incidence and severity of tuberculosis. In this country few people need be chronically malnourished. Nevertheless, serious malnutrition may result from gastrointestinal disorders, food fads, food idiosyncracies, and the desire of young women to have sylphlike figures.

In the following case reports are presented illustrative examples of the temporal relation between unexpected changes in the course of pulmonary tuberculosis and the existence of certain factors which may play an important part in initiating the particular exacerbation or remission of the illness.

CASE REPORTS AND COMMENTS

Trauma to the chest is considered capable of causing activation of an inactive lesion of tuberculosis, either by providing an area of traumatized tissue for the localization of blood-borne bacilli or by the mechanical rupture of a quiescent tubercle.

Case 1 (K. S. N.). The patient was a 55-year-old man who had had left-sided chest pain on inspiration intermittently for thirty years. In September 1946 he fell and struck his left

[1] From the Veterans Administration Hospital, Butler, Pennsylvania.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

chest against the edge of a chair. The following day he noted severe chest pain on the left, aggravated by deep breathing. A few days later he developed fever and dyspnea. He was admitted to the hospital three weeks later. His temperature was 101°F. and he had a pleural effusion on the left side. Thoracentesis yielded serous fluid which on culture was repeatedly found to contain tubercle bacilli. He received streptomycin for six weeks, at which time the drug was stopped because of exfoliative dermatitis. The pleural fluid disappeared after a few months. The lungs were normal at that time, and examination of the sputum and gastric aspirates was negative. In May 1948, however, a small lesion appeared on the right side and at this time cultures of gastric aspirates became positive. The lesion slowly regressed. The cultures of gastric aspirates became negative in September 1948 and have remained negative. The patient was discharged in June 1949, his disease arrested.

Intercurrent disease is thought sometimes to cause a reactivation of an apparently arrested lesion. Pneumonia, measles, influenza, and pertussis have been mentioned in this regard, but the mechanisms by which they may accomplish this reactivation is not understood. Primary or metastatic carcinoma of the lung may cause a similar activation. Conceivably the invading carcinoma destroys the fibrous or calcific areas surrounding the tubercle bacilli and thus mechanically frees the bacilli.

Even less tangible is the adverse effect of mental or emotional stress on resistance to tuberculosis. This effect may be produced by loss of sleep, loss of appetite, the effects of psychic trauma, or other mechanisms which are equally poorly understood. It has been thought that emotional stresses may precipitate exacerbations of tuberculosis. Proof of this is lacking. All patients have such disturbances, and in some the tuberculosis becomes worse, while in others it does not. Nevertheless, in some instances the time relationship between the emotional disturbance and exacerbation of the patient's tuberculosis is a striking one. The following case reports are examples of acute exacerbations of tuberculosis appearing immediately after emotional stress. It must be emphasized that there is no proof of causation other than the close relationship in point of time.

Case 2 (C. E.). The patient was a 26-year-old woman who was married and had two children. She was admitted with minimal pulmonary tuberculosis, the lesion being restricted to the left infraclavicular region. No cavity was visualized roentgenographically, but culture of a sputum specimen was positive. On strict bed rest the lesion regressed and the sputum cultures became negative. She was gradually allowed more activity, becoming fully ambulant after six months. She continued to do well for two months longer. She became friendly with one of the male patients to such good purpose that, when her next period was delayed, she feared she was pregnant. This proved not to be true, but the damage done by several weeks of intense worry could never be repaired. The pulmonary lesion progressed, the sputum cultures became positive again, and a cavity developed. Pneumothorax was attempted but was unsuccessful. Although cavity closure was achieved by thoracoplasty, spread to the right lung occurred and her downhill course continued. The patient died less than two years after admission and about one year after the benign course of her disease was reversed during a period of emotional stress.

Case 3 (V. D.). The patient was a 52-year-old man who had had chronic pulmonary tuberculosis since 1922. He had refused to go to a sanatorium and had worked and supported his family. He got along well with his wife and daughter. His disease grew worse in September 1943, and in March 1944 he was admitted to the hospital. He did well in the hospital. The

pulmonary lesion regressed, his symptoms diminished, he gained weight, and his sputum cultures became negative.

In the fall of 1946 he began to realize that something was wrong between him and his wife. On her next visit the matter was discussed. His wife admitted that she had changed and asked him to allow her to obtain a divorce, alleging "mental cruelty and abusive treatment." He promptly left the hospital (January 1947) and returned home. His wife refused to take care of him, and their 21-year-old daughter took her mother's part. Thereafter he discovered that his wife was unfaithful. By this time the patient's symptoms had recurred and he had developed sore throat and dysphagia. A few weeks later he was admitted to the hospital. His pulmonary disease had progressed in the interim. On admission he was febrile, and laryngeal examination showed lesions characteristic of tuberculous laryngitis. Examination of a specimen of sputum was positive for acid-fast bacilli. The patient agreed to drop charges on condition that his wife drop her divorce suit against him, that she would not contest his suit for divorce, and would give up her claim to any part of his property. She agreed to do all of this. He was reconciled to his daughter. At that time, with all of his problems solved insofar as he could solve them, he relaxed and became a model patient. His subsequent course was uneventful. Successive laryngeal examinations and chest roentgenograms showed steady improvement, the sputum cultures once more became negative, and in fifteen months he was discharged with apparently arrested disease.

Case 4 (K. L.). The patient was a 30-year-old man admitted October 30, 1947 with a history of illness of one week's duration. The onset was acute, with chills, cough, expectoration, and temperature of 103°F. A roentgenogram showed a moderately advanced lesion scattered through the lower half of the right lung, exudative in character, without cavitation. He was treated by bed rest, phrenic crush, pneumoperitoneum, and streptomycin. On this regimen he improved. His temperature came down gradually to normal within two months, his cough and expectoration diminished, and he gained weight. Roentgenograms showed some improvement until July and were then stationary until September. A roentgenogram on November 16, 1948 showed marked progression of disease on the right, with cavitation and a new lesion on the left.

Questioning revealed that the patient came from an unusually close-knit family. In July 1948 his mother bought a house, using borrowed money. A single brother, of whom he was very fond, was depended on to help with the payments. This brother had suddenly started drinking heavily, and was dissipating his money, endangering his job, and ruining his own and his family's standing in the community. This conduct was considered of sufficient importance for an older brother to leave town and change his name in an effort to escape the disgrace. The patient was seriously disturbed about his mother's financial problems, about "what is happening to my brother," as well as the family's shame.

After repeated discussions, the patient was made to understand that his duty to his family as well as his own interest required his best effort to get well and that life was worth living even if his brother's conduct was unbecoming. His pension money was sufficient to take care of expenses on his mother's house. Simultaneously, news was received that the brother was behaving better. The patient was then able to relax again. Pneumothorax was instituted on the left. Since March 1949 he has gained weight and the pulmonary lesion has regressed. The lesion on the left side now appears to be well controlled and, although the cavity at the right base is still patent, he is doing well clinically and his prognosis is considered good.

Case 5 (W. P. P.). This patient was a 24-year-old man who was admitted to the hospital on November 24, 1948 with an extensive tuberculous lesion in the left lung. His temperature was normal and his appetite was good. Pneumoperitoneum was induced uneventfully on January 11, 1949. When no significant clearing resulted, it was decided to do a thoracoplasty. On March 26 his fiancée broke their engagement. On April 4 his temperature was 99.2°F. and during the next ten days averaged 99.8°F. On April 16 his temperature reached 105.2°F. and there was inspiratory pain in the left chest. A roentgenogram of the chest showed a

massive spread of disease on the left. The patient was placed on strict bed rest, was given 1 gm. of streptomycin daily for ninety days. After a time he was able to see his broken engagement in its proper perspective. His temperature gradually returned to normal and, inasmuch as his right lung has remained normal, a thoracoplasty on the left is once more being considered.

DISCUSSION

The case histories presented above are in no way unique. They do, however, illustrate part of the basis for the impression that external factors may significantly alter the course of tuberculosis. In Case 1, the change from inactivity to activity followed trauma to the chest. In Cases 2, 3, 4, and 5, the reasons for the change were less obvious. In each instance an important emotional problem was found and in 3 of the 4 cases a solution of the emotional problem was followed by improvement of the disease. It seems likely that in many patients in whom unexplained exacerbations in the course of pulmonary tuberculosis occur, careful and sympathetic questioning would yield the information that some problem had arisen to disturb the patient emotionally, and satisfactory solution of that particular problem might prove to be of significant benefit.

SUMMARY

A group of case histories are presented to illustrate the temporal relation between exacerbations and remissions of chronic pulmonary tuberculosis and various events in the patients' life situations. Although direct proof of causation is lacking, it is believed that the physician who treats such patients as those reported here may neglect an important feature of the therapy if he fails to attempt solution of the patients' emotional problems.

Case Reports

SPONTANEOUS HEMOPNEUMOTHORAX[1]

Report of Two Cases

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(Received for publication June 30, 1950)

INTRODUCTION

The sudden accumulation of air and blood in the pleural cavity resulting from spontaneous pneumothorax with hemorrhage without antecedent trauma, and in the absence of tuberculosis or other active pulmonary disease, is a rare but distinct clinical entity of serious import. The first case was described by Pitt (1) in 1900. In 1942 Hartzell (2) reviewed the literature. He collected 40 cases and added 4 others. In another study of the earlier literature, Dorset and Terry (3) discovered 4 additional cases. Since 1942, 13 cases have been reported (3–14). The medical literature has thus revealed reports of 61 cases of this condition. Fourteen of these patients have died, a case fatality of 23 per cent. It would seem desirable to add to the published experience when appropriate cases are encountered, especially in view of the seriousness and apparent rarity of the condition.

The purpose of this paper is to describe 2 additional cases of spontaneous hemopneumothorax encountered on the services of the Departments of Medicine and of Preventive Medicine and Student Health of the University of Wisconsin Medical School.

CASE REPORTS

Case 1. This patient was a 20-year-old university student who was a native and resident of Baghdad, Iran until coming to this country in 1946. He had been well until the onset of the present illness. On January 20, 1949, twenty-four hours before admission to the hospital, while sitting reading quietly he noted a sudden, severe pain in the right side of the chest anteriorly, radiating to the back on the same side. There had been no undue exertion prior to the onset. The pain gradually became more severe during the day, but was relieved somewhat in the evening by local application of heat. The following day the pain recurred and was aggravated by deep inspiration. He complained also of light-headedness and nausea. There was no history of parasitic disease. The Mantoux test had been negative two years previously. The blood count was normal at that time. There was no history of tuberculosis in his family.

On admission to the hospital the patient did not appear acutely ill. There was slight respiratory distress and he was extremely apprehensive. The blood pressure was 120 systolic and 78 diastolic in mm. of mercury, pulse rate was 120 per minute, and the respiratory rate, 22 per minute. The trachea was in the mid-line. There was decreased expansion, absent fremitus and breath sounds, and shifting dullness over the lower right chest. There was marked hyperresonance of the right upper thorax in the upright position and over the entire right anterior thorax in the supine position. Breath sounds over this area were diminished. There was no succussion splash. Moderate rigidity of the right upper quadrant of the abdomen was present.

Examination of the blood revealed 12.0 gm. of hemoglobin per 100 cc., 4,730,000 erythro-

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cytes per cu. mm., and 14,500 leukocytes per cu. mm. On differential count, 68 per cent of the leukocytes were neutrophils; 30 per cent, lymphocytes; 3 per cent, eosinophils; and 1 per cent, monocytes. The sedimentation rate (Wintrobe, corrected) was 16 mm. per hour. Bleeding time, coagulation time, clot retraction, and platelet count were normal. A tuberculin skin test using 1 mg. of Old Tuberculin was negative. The histoplasmin skin test was negative. A roentgenogram of the chest taken on January 21, 1949 revealed a moderate pneumothorax on the right with fluid in the basal quarter of the pleural cavity. The lung above this level was fairly well expanded except for a wedge of atelectasis in the central portion. The left lung was normal (figure 1).

The day following admission 1,000 cc. of fluid was aspirated from the right chest. This fluid had the appearance of whole blood but did not clot. Cultures for tubercle bacilli were negative. Thoracenteses were performed on each of the three succeeding days, yielding 500, 100, and 50 cc., respectively. There was concomitant improvement in the roentgenographic appearance of the right lung. By the eleventh hospital day the lung had re-expanded to the parietes laterally with only a small pneumothorax remaining at the apex and in the lower costophrenic sulcus. The amount of fluid decreased so that the mid-portion of the diaphragm was visible (figure 2). The patient's general condition was satisfactory except for a daily afternoon fever to 100.6°F., moderate anxiety, and occasional pain in the right chest. Seventeen days after admission he was allowed to leave the hospital for several hours. On that day chest pain increased and pleural fluid reaccumulated (figure 3). Afternoon fever continued for three weeks. Penicillin and streptomycin therapy was not followed by any demonstrable effect. On the twenty-first hospital day 500 cc. of brownish fluid resembling old blood were removed. The roentgenographic appearance of the lung improved slowly during the period of bed rest. By March 8, seven weeks after admission, pleural thickening along the periphery well up toward the apex was the only significant abnormality. On February 15 the hemoglobin was 10.9 gm. per 100 cc. There were 4,440,000 erythrocytes per cu. mm., 11,200 leukocytes per cu. mm., with 15 per cent eosinophils in the differential count. The sedimentation rate was 38 mm. per hour. On March 7 the hemoglobin was 12.4 gm. per 100 cc.; erythrocytes, 4,580,000 per cu. mm.; leukocytes, 8,900 per cu. mm., with 18 per cent eosinophils. The eosinophilia was unexplained. Repeated stool examinations did not reveal intestinal parasites. (In a differential count obtained three weeks before onset of the present illness there were 7 per cent eosinophils.) The patient was discharged on March 13, 1949. When last seen on December 31, 1949 he was in excellent health. He occasionally had sharp pains in the right chest, but this symptom disappeared early. Roengtenogram of the chest showed only minimal pleural thickening (figure 4). There was no evidence of residual disability.

Case 2. The patient was a 23-year-old farmer who was admitted to the Wisconsin General Hospital without complaint on January 16, 1948. Twelve days previously he had awakened with "backache" in the left thoracic area. Several hours thereafter, while lifting a milk can which weighed approximately 115 pounds, he suddenly experienced a "bubbling sensation" in the left side of the chest. Dyspnea and weakness ensued and he went to bed. When seen some hours later he was in a state of shock with a pulse rate of 160 per minute and respiratory rate of 44 per minute. He was transferred to the local hospital where intravenous fluids, adrenal cortical extract, penicillin, and oxygen were administered. He improved following this therapy. On the ninth day of illness 400 cc. and, on the eleventh day, 500 cc. of grossly bloody fluid was aspirated from the left chest. His temperature ranged from 99°F. to 101°F. during the first twelve days of illness.

On admission to this hospital on January 16, 1948, he was somewhat pale but in no distress. There was decreased expansion and fremitus, shifting dullness, and absent breath sounds over the left lower thorax. There was egophony immediately above this level. There was an area of hyperresonance in the superior portion of the left chest. A succussion splash could not be detected.

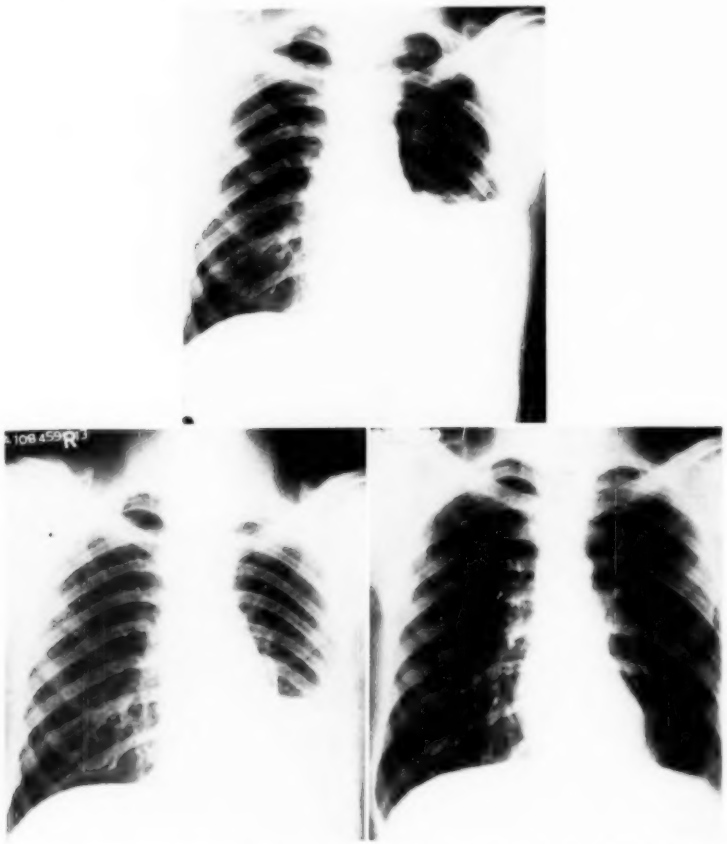
Blood studies on January 18 revealed 13.3 gm. of hemoglobin per 100 cc., 4,600,000 eryth-

rocytes per cu. mm., and 12,800 leukocytes per cu. mm. Bleeding time, coagulation time, and capillary fragility test were normal. The tuberculin skin test (0.1 mg. of OT) was negative. The histoplasmin skin test (0.1 mg.) was positive. Smears and cultures of the sternal

FIGS. 1–4. Case 1. (Upper left) Chest roentgenogram twenty-four hours after onset of right spontaneous hemopneumothorax. (Upper right) Roentgenogram of chest on the eleventh day shows clearing of fluid and re-expansion of right lung following thoracenteses. (Lower left) Sudden increase in pleural fluid on the twentieth hospital day. (Lower right) Appearance of chest eleven months after onset. Only minimal pleural thickening remains.

marrow were negative for *Histoplasma capsulatum* as were cultures of the pleural fluid. The roentgenogram of January 17, 1948 showed pneumothorax with fluid accumulation in the lower half of the lung field on the left extending to the third interspace anteriorly. The upper lobe of the lung was collapsed approximately 50 per cent (figure 5). The vital capacity was 2.4 liters.

Thoracenteses were performed on the second, fourth, fifth, and eighth hospital days. A total of 4,000 cc. of bloody fluid was removed. There was progressive re-expansion of the left upper lobe, and by the thirteenth hospital day it was well expanded. The lower lobe



FIGS. 5-7. Case 2. (Top) Roentgenographic appearance on admission to hospital thirteen days after onset of illness. Left hydropneumothorax is present. (Lower left) Twenty-seven days after onset. The lung is expanded except for an area of persistent atelectasis at the left base medially. (Lower right) Appearance of chest five months after onset. Only minimal pleural thickening remains.

remained poorly aerated and was compressed to a triangle at the base medially (figure 6). It seemed likely that this lobe was bound down by thickened pleura. At bronchoscopy patent left lower lobe bronchi were visualized. The patient's temperature was elevated occasionally to 100°F. in the afternoon. Because of the failure of expansion of the left lower lobe, thoracotomy was performed on February 9, 1948, the thirty-sixth day after onset.

The lung was found to be densely adherent to the chest wall and diaphragm in a number of places. There was evidence of old hemothorax. There was only partial expansion at the base. The left lung was encased in a thin organizing peel. At the apex there were two bullous lesions approximately 1.5 cm. in diameter and one on the posterior lateral aspect of the lower lobe was approximately 3 cm. in diameter. Complete decortication was performed and the bullae were punctured and sutured. The patient pursued an uneventful postoperative course and was discharged on the ninth postoperative day. When last seen, on May 18, 1949, he was in excellent health. A roentgenogram of the chest at that time showed complete expansion of the left lung and only minimal pleural thickening along the periphery (figure 7).

DISCUSSION

In the two cases of hemopneumothorax described, the origin of the bleeding was not determined. In one case (Case 2) pleural bullae were discovered at thoractomy. Several investigators have considered lesions of this type to be significant in the pathogenesis of the condition. The most convincing evidence for this view is to be found in a review by Helwig and Schmidt (10) who noted emphysematous bullae in 10 of 14 cases examined at autopsy, with demonstrable rupture of these lesions in 4 of them. Another mechanism may be the tearing of richly vascularized adhesions between visceral and parietal pleura by traction during collapse of the lung at the time of spontaneous pneumothorax. Torn pleural adhesions were found in 5 of 14 of the cases studied post mortem (10). This mechanism seems to us to be the most logical explanation for the majority of instances.

Clinically, these 2 cases resembled those previously reported. The onset was typical of that of the usual form of spontaneous pneumothorax. In both patients the onset of chest pain was sudden, and both had been well previously. There was associated weakness, mild dyspnea, and, in one case, shock in a few hours. The physical and roentgenographic findings were those of hydropneumothorax. Fluid having the appearance of whole blood which did not clot was aspirated from the chest. The currently accepted explanation for the incoagulability of blood in the pleural cavity is ascribed to Trousseau who believed that blood clotted rapidly in the pleural cavity but was defibrinated by the movement of the lungs and heart and the fibrin was precipitated on the pleural surfaces. This view was supported by finding during thoractomy in Case 2 a peel of fibrin which enveloped the lung. Complete re-expansion of the lung without thoracotomy, as occurred in Case 1, has been the usual course of events in those patients who survive the initial shock and/or mediastinal compression.

Rational treatment consists initially of measures to combat shock. The question then arises of the advisability of early aspiration of large quantities of blood from the pleural cavity. In theory, this procedure might reduce intrathoracic pressure sufficiently to increase the hemorrhage. Other considerations seem to offset this potential hazard. Failure to remove the blood may result in mediastinal compression early in the course, or provide opportunity for encapsulation and fibrosis with failure of expansion of the involved lung. This can progress to calcification of the pleura (15). Fibrin encapsulation of the lung with compression atelectasis occurred in Case 2. This was corrected by decortication. In this patient, nine days elapsed before the first thoracentesis was performed. It would seem wise to attempt to re-expand the collapsed lung by aspiration of blood and air as soon as hemostasis has occurred.

SUMMARY

Two cases of spontaneous hemopneumothorax are presented, and the typical features of this unusual, dramatic, and serious condition are described.

One patient was treated on the second day by the removal of blood and air from the thoracic cavity. He recovered and the lung re-expanded spontaneously. He has remained completely well for one and one-half years. The other patient developed lower lobe compression atelectasis due to fibrosis of the pleura. Re-expansion was accomplished by decortication. In this patient, early aspiration of blood from the thoracic cavity was not attempted.

SUMARIO

Hemoneumotórax Espontáneo

Los dos casos presentados son de hemoneumotórax espontáneo. Descríbense además las características de este estado extraño, dramático y grave. Un enfermo fué tratado el segundo día con la extracción de sangre y aire de la cavidad torácica. Repúsose y el pulmón se reexpandió espontáneamente, continuando el enfermo absolutamente bien por espacio de año y medio. El otro paciente manifestó atelectasia por compresión del lóbulo inferior, debida a fibrosis de la pleura. La reexpansión se obtuvo por medio de la decorticación, sin que se probara en este caso la aspiración temprana de la sangre de la cavidad torácica.

REFERENCES

(1) Pitt, G.: A case of a rapidly fatal haemopneumothorax apparently due to the rupture of an emphysematous bulla, Tr. Clin. Soc. London, 1900, *33*, 95.

(2) Hartzell, H. C.: Spontaneous hemopneumothorax: Report of three cases and a review of the literature, Ann. Int. Med., 1942, *17*, 496.

(3) Dorset, V. J., and Terry, L. L.: Spontaneous hemopneumothorax with recovery, Am. J. Med., 1949, *6*, 135.

(4) Tannenbaum, M.: Spontaneous hemopneumothorax with report of a case, Dis. of Chest, 1942, *8*, 178.

(5) Snively, D., Shuman, S., and Snively, W. D.: Spontaneous hemopneumothorax: Report of a case, Ann. Int. Med., 1942, *16*, 349.

(6) Lea, R. G.: Spontaneous haemopneumothorax, Canad. M. A. J., 1942, *42*, 371.

(7) Payn, S. B., and Lief, V. F.: Spontaneous hemopneumothorax: Report of a case, Bull. U. S. Army M. Dept., 1945, *3*, 94.

(8) Franklin, J.: Spontaneous hemopneumothorax: Report of a case occurring in a soldier, Ann. Int. Med., 1945, *23*, 437.

(9) Vander Meer, R.: Spontaneous hemopneumothorax: A case report, Am. Rev. Tuberc., 1946, *54*, 283.

(10) Helwig, F. C., and Schmidt, E. C. H.: Fatal spontaneous hemopneumothorax, Ann. Int. Med., 1947, *26*, 608.

(11) Waring, J. J.: Spontaneous hemopneumothorax, Clinics, 1945, *4*, 940.

(12) Nalls, W. L., and Matthews, J. H.: Idiopathic spontaneous hemopneumothorax, Dis. of Chest, 1949, *15*, 612.

(13) Kertesz, G. J.: A case of spontaneous hemopneumothorax, Journal-Lancet, 1950, *70*, 143.

(14) Elrod, P. D., and Murphy, J. D.: Spontaneous hemopneumothorax treated by decortication, J. Thoracic Surg., 1948, *17*, 401.

(15) Milhorat, A. T.: Spontaneous haemopneumothorax, Am. Rev. Tuberc., 1937, *35*, 106.

CHRONIC MILIARY TUBERCULOSIS[1, 2]

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INTRODUCTION

The purpose of this communication is to report a case of chronic miliary tuberculosis, with involvement of lungs, eye, larynx, kidney, anus, and subcutaneous tissue. The patient was observed over a period of almost three years, at the end of which time all lesions were improved, and most of them arrested.

CASE REPORT

The patient was a 50-year-old white male who, in November 1946, noticed the gradual onset of hoarseness and slight pain on swallowing. He also noticed a tiny red spot on his left eyeball which seemed to be increasing in size. By March 1947 there was definite loss of visual acuity in the left eye and there had been no improvement in hoarseness. During this period he had lost ten pounds in weight. He was admitted to Veterans Administration, Medical Teaching Group, Kennedy Hospital, March 27, 1947, for biopsy of the nodule on the left sclera.

Physical examination on admission revealed a middle-aged white male in a fair state of nutrition, who spoke with slight hoarseness. There were palpable lymph nodes in the left cervical and in both inguinal regions. A soft tissue mass, 3 cm. in diameter, was felt in the left axilla. This mass was not tender and did not adhere to the skin. A similar mass was palpated at the inner border of the left scapula. Physical examination of the chest was negative. Liver dullness extended 1 cm. below the right costal margin. There was a draining fistula-in-ano. Indirect laryngoscopy revealed a thickened, inflamed, right aryepiglottic fold and a shallow ulcer in the supraglottic region. There was an ulcerated nodule, 7 to 8 mm. in diameter, surrounded by dilated vessels in the temporal sclera of the left eyeball adjacent to the cornea.

The patient had been a chronic alcoholic for approximately eight years, and had had what he called a "cigarette cough" for approximately seven years. In 1920 he had a primary chancre and gonorrhea as well as inguinal buboes which required incision and drainage. Treatment of his syphilis had consisted of approximately nine injections of neosalvarsan and bismuth.

Laboratory studies: Urinalysis and complete blood count were within normal limits. The sedimentation rate was 20 mm. per hour. Serologic test for syphilis was negative. Direct smear of the sputum was positive for acid-fast bacilli and tubercle bacilli were recovered in cultures. The blood nonprotein nitrogen was 27 mg. per 100 cc. The urea clearance test was normal. Results of liver function tests were within normal limits. Examination of a specimen of cerebrospinal fluid revealed a negative Kolmer test and a normal colloidal gold curve. The values of chemical determinations were all within normal limits. Roentgenogram of the chest (figure 1) showed a dense mottled infiltration throughout both lung fields, heaviest in the mid-lung fields and clearer at the bases. No large cavities were present, but there

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[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

were scattered small areas of radiolucency. There was blunting of the right costophrenic angle and thickening of the pleura over the base of the right lung. The soft tissues and bony thorax appeared normal.

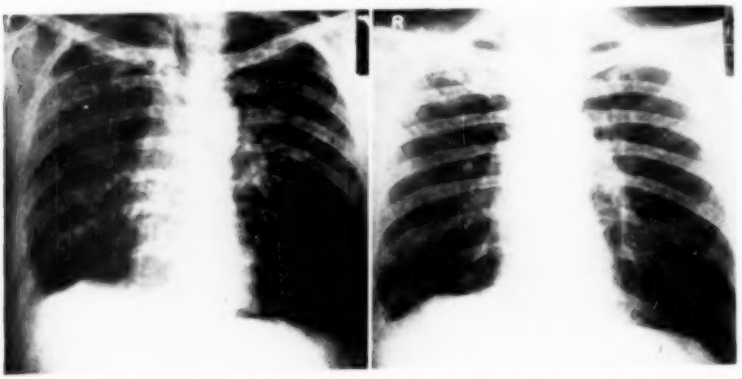

FIG. 1. (Left) Roentgenogram of the chest, March 31, 1947, at the time of admission to the hospital, showing widespread pulmonary infiltration.

FIG. 2. (Right) Roentgenogram of the chest, July 29, 1949, showing marked resolution of the pulmonary infiltration.

FIG. 3. (Left) Photograph of the eye, April 14, 1947, immediately after excision of the tuberculoma.

FIG. 4. (Center) Photograph of the eye six months after admission, October 7, 1947, when the destruction was at its maximum.

FIG. 5. (Right) Photograph of the eye four months before discharge, June 14, 1949, showing the marked progress in healing.

Clinical course: On March 31, 1947, the nodule on the left eyeball was excised. The sclera beneath the nodule had been completely destroyed, exposing the underlying uveal tissue in an ovoid area approximately 1 by 1.5 cm. Microscopic examination of the specimen showed tuberculous granulation tissue. Streptomycin therapy was instituted April 23, 1947

with 2 gm. per day in divided doses and was continued for 120 days. Because of the occasional presence of albumin, leukocytes, and erythrocytes in his urine, cultures of numerous specimens were done, and some were reported positive for tubercle bacilli. The mass on the back, which was considered to be a cold abscess, enlarged rapidly. Aspiration yielded only approximately 1 cc. of purulent material, and the mass was excised after it had grown to a diameter of 15 cm. The report of the pathologic examination was "necrotic debris." No tuberculous granulation tissue was found but acid-fast bacilli were present on direct smear of the debris, and cultures of the material yielded tubercle bacilli. After only approximately one week of streptomycin therapy, there was definite improvement in the laryngeal lesion and it was completely healed within a month.

At cystoscopy, urine was collected from each ureter and cultures were inoculated separately. Tubercle bacilli were cultured from the left ureteral specimen. Retrograde pyelog-

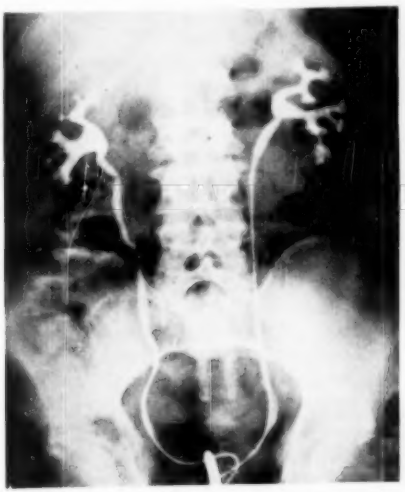

FIG. 6. Retrograde pyelogram showing the destructive process in the left kidney.

raphy (figure 6) revealed partial destruction of the lower minor calyx of the left kidney. Because of this renal lesion, a second course of streptomycin was given in a dosage of 0.25 gm. twice a day for 42 days, from August to October 1948. There had been gradual clearing of the pulmonary infiltration, especially that of the left lung. Progress of the lesion in the eye had also been satisfactory. In addition to streptomycin, treatment of the eye consisted only of local instillation of atropine. The inflammatory reaction about the lesion remained moderately active for the first six months of treatment, with associated caseation necrosis of the scleral margins, but at that time it began to show signs of healing. This was manifested by a very gradual decrease in the injection about the wound, thickening of the membrane covering the exposed uveal tissue, flattening of the staphyloma which was present, and slow absorption of the caseous material about the scleral margins of the wound. At the height of the local process there was a staphyloma projecting approximately 4 to 5 mm. above the surrounding sclera and cornea and considerable distortion of the anterior portion of the globe due to destruction of the sclera. There was no involvement of the uveal or intraocular tissues other than a moderate inflammatory reaction. By June 1949 the membrane covering the wound was dense and the staphyloma had become flat. There remained

only a few dilated vessels, and there was very little distortion of the globe (figures 3, 4, 5). His corrected vision was 20/25.

After the conclusion of the second course of streptomycin, tubercle bacilli could still be grown in cultures of the urine. At this time, the tubercle bacilli were resistant to 1,000 γ of streptomycin per cc. A left nephrectomy was performed October 13, 1948. Pathologic examination of the kidney specimen revealed a necrotic caseous mass at one pole, which on microscopic examination showed the typical morphology of tuberculous granulation tissue. Urine cultures were negative for tubercle bacilli following operation and remained negative. Convalescence was uneventful.

The patient left the hospital October 8, 1949 against medical advice. At the time of discharge his pulmonary disease was arrested. Examination of sputum smears had been negative for acid-fast bacilli for sixteen months. The chest roentgenogram (figure 2) had been stationary for one year. Urine cultures had been negative for tubercle bacilli since the nephrectomy one year before discharge. The eye had shown remarkable improvement and was continuing to heal, with progressive improvement in vision.

DISCUSSION

Until about 1920, miliary tuberculosis was considered to be invariably fatal. Since that time, a series of papers have appeared describing chronic cases and occasionally healed cases. Any instance of survival of more than three months has been classed as chronic miliary disease (1). From the work of Wilson (2) and others, it seems probable that in all forms of tuberculosis there may be periods of transient bacillemia. Such episodes may result in acute generalized miliary tuberculosis with a rapidly fatal issue or may be followed by no clinically demonstrable lesion. Between these extremes are the cases of chronic miliary tuberculosis and others with hematogenous lesions of a more varied and unusual nature (3). Such patients may live many years, although they usually die from the consequences of recurrent bacillemia. A few have been known to survive throughout a normal life span (4, 5, 6). The patient reported herein was still alive in October 1949, three years after the apparent onset of his illness, and he appeared to be in excellent general condition. The tuberculoma of the sclera and the necrotic lesions of subcutaneous tissue which were present in this patient are among the more unusual manifestations of this disease.

The pathogenesis of chronic miliary tuberculosis remains a subject of controversy. Zavod (7) and others have suggested that in some instances bacillemia is limited to the lesser circle of the cardiovascular system, due to the ability of the lungs to filter out the microorganisms and thereby prevent their entrance into the systemic circulation. In such a case, the result is clinically manifest only as a pulmonary miliary tuberculosis. In this patient, the presence of undoubted hematogenous lesions in the eye, kidney, and subcutaneous tissue makes it necessary to modify the above hypothesis to the extent of assuming the filter to be less effective, or the microorganisms more numerous and virulent.

Chronic miliary tuberculosis may be regarded as the result of a balance between the number and virulence of the bacilli gaining entrance into the blood stream and the general resistance of the host as well as that of the individual organs attacked. Repeated studies (8) in guinea pigs have shown that the heavier the inoculum used to produce the experimental infection, the greater will be the extent and rate of spread throughout the body. Willis (9) injected tubercle bacilli into the nutrient artery of a long bone in guinea pigs, and found that in previously uninfected animals he produced a generalized dissemination, but that in allergic, previously infected animals, he produced merely a local tuberculosis of that bone. Rich (10) compared the degree of involvement of different human tissues in miliary tuberculosis, and found marked differences in such organs as the thyroid, kid-

ney, liver, and lung. In man, the almost invariable occurrence of caseous lymph nodes in chronic miliary tuberculosis strongly suggests that they are the most common foci from which dissemination takes place, probably by way of the lymphovenous circulation. The bacilli may enter the lymphatics which empty into the veins and thus be conveyed to the right side of the heart. Direct rupture of a caseous lesion into a blood vessel and venous intimal ulcerative tuberculosis are probably less common methods of hematogenous dissemination in cases of this sort. In our patient, we were unable to identify the source of bacillemia. If we assume that a caseous lymph node was present as the basis for his disease, it is possible that the beneficial effect of streptomycin was exerted in controlling the disease in the lymph node, thus preventing further bacillemia and dissemination.

Conceivably, the severe tuberculous laryngitis in this patient may have given rise to a widespread bronchogenic dissemination, with a roentgenographic picture similar to that of the pulmonary miliary disease. A caseous focus in the larynx, or perhaps the lungs, might then have been the source from which transient invasions of the blood stream occurred, resulting in the genesis of the other lesions described. In support of this theory, the appearance of the roentgenograms suggests the presence of an older infiltration in the upper right lung field from which the laryngitis might have arisen as a complication. The first explanation, based on the more common pathogenesis, appears the more likely.

The final results of treatment in this patient, although for the most part slow in onset, were extremely gratifying. Lesions of the larynx and anus showed the usual prompt response to streptomycin. The lung lesions took considerably longer, but gradually cleared almost completely, perhaps confirming thereby the impression that the lesions were hematogenous. The renal lesion relapsed after initially improving, and finally required nephrectomy, as would be expected. The subcutaneous tuberculous mass was excised early in the course of treatment and never gave rise to further difficulty. The result obtained in the eye was especially impressive as such lesions previously invariably led to ocular destruction (11).

The widespread character of the disease, the unusual types of tuberculosis exemplified, and the subacute course make this case of more than usual interest. The steady but slow improvement under antimicrobial therapy was probably due in good part to the action of streptomycin upon the various lesions themselves, and perhaps also to the prevention of further episodes of bacillemia by the healing of the causative focus promoted by the drug. The special problems which arose because of the widely different tissues attacked made necessary a prolonged multiple therapeutic approach which required the services of a team of consultants in fields other than tuberculosis in order to achieve the satisfactory result obtained.

SUMMARY

A case report is presented of a patient with chronic miliary tuberculosis, in whom lesions were present in the eye, anus, subcutaneous tissue, larynx, kidney, and lungs. Following administration of streptomycin and surgical treatment of the eye and kidney all lesions exhibited a satisfactory response.

The features of chronic miliary tuberculosis are discussed briefly.

SUMARIO

Granulia Crónica

Esta historia clínica es de un enfermo con granulia crónica, en el que había presentes lesiones en el ojo, ano, tejido subcutáneo, laringe, riñón y pulmones. A continuación de la

administración de estreptomicina y del tratamiento quirúrgico del ojo y riñón, todas las lesiones manifestaron una respuesta satisfactoria.

Repasanse brevemente las características de la granulia crónica.

REFERENCES

(1) Hinzelman, W. J.: Chronic miliary tuberculosis, Rocky Mountain M. J., 1940, *37*, 508.
(2) Wilson, G. S.: Tuberculous bacillemia, Medical Research Council, Special Report Series No. 182, London, 1933.
(3) Grethman, W.: Protracted multiform tuberculosis, Nat. Tuberc. A. Tr., 1936, p. 80.
(4) Rubin, E. H.: Hematogenous tuberculosis in adults, Am. Rev. Tuberc., 1939, *40*, 667.
(5) Simmonds, F. A. H., and Pagel W.: Chronic disseminated tuberculosis, Brit. M. J. 1938, *1*, 15.
(6) Billard, E. W.: Hematogenous tuberculosis, New York State J. Med., 1939, *39*, 1670.
(7) Zavod, W. A.: Hematogenous pulmonary tuberculosis, J.A.M.A., 1937, *109*, 1693.
(8) Soltys, M. A., and Jennings, A. R.: Dissemination of tubercle bacilli in experimental tuberculosis in the guinea pig, Am. Rev. Tuberc., 1950, *61*, 399.
(9) Willis, H. S.: Studies on tuberculous infection, Am. Rev. Tuberc., 1925, *11*, 439.
(10) Rich, A. R.: Pathogenesis of Tuberculosis, Charles C Thomas, Springfield, Ill., 1944, p. 318.
(11) Maiden, S. D.: Solitary tuberculoma of the sclera in a patient with multiple advanced systemic lesions, treated with streptomycin, Am. J. Ophth. (in press).

Editorial

Antihistaminics and the Tuberculin Reaction

During the past two years the subject of antihistaminics and the tuberculin reaction has appeared in the REVIEW six times, either as an original article or as a letter to the editors, not to mention the several abstracts on the subject which have been printed. A perusal of these articles leaves the reader confused by the contradictory character of the reported results and with a desire for a definite answer to the question as to whether or not the administration of antihistaminic drugs does have an effect on the tuberculin reaction.

A definitive answer could probably be given if there were available a background of fundamental research based on experimental animals. Unfortunately the one carefully documented study of the effect of antihistaminics on the tuberculin reaction of tuberculous guinea pigs (Am. Rev. Tubere., 1948, *57*, 504) cannot be used as a basis of comparison with the studies in man since the antihistaminic (Benadryl) was given parenterally and in relatively enormous doses (50 mg. per kg.). In all of the studies on humans the various antihistaminics have been given by mouth.

A possible explanation for the varied results reported following the trial of antihistaminics in man is that different drugs have been used. One could not predict that an effect of one of these compounds could be duplicated by another compound of this group. Furthermore, the dose of drug employed and the length of time it was administered have varied markedly.

The suggestion has been made that one would not expect drugs recommended for use in the anaphylactic type of allergic reaction to have much effect on the delayed, tuberculin type of reaction. This is the point of view of the majority of the articles already printed in the REVIEW and would lead one to agree with the writers of the article in the current number that "Antihistaminic medications in the usual clinical dosages . . . have no effect on the tuberculin test. . . ."

The possibility that long-continued therapy with antihistaminics may depress the level of skin sensitivity to tuberculin has been coupled with the more important claim of a beneficial effect on the course of pulmonary tuberculosis in a number of cases (Ann. Allergy, 1949, *7*, 306). This claim must be viewed with the proper scientific skepticism. The antihistaminic drugs in general are known to have an atropine-like effect, and any observed decrease in the cough or the amount of sputum produced by a patient might be due to this side effect. Attempts to evaluate the "sense of well-being" of the patient and changes in the roentgenogram are notoriously difficult. Those who have had experience in evaluating the merits of streptomycin therapy in tuberculosis realize the long and difficult road to be traversed before any chemotherapeutic agent can be accepted as beneficial in the treatment of tuberculosis.

C. EUGENE WOODRUFF

AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

Report of Dr. H. McLeod Riggins, Chairman of the Committee on Medical Research and Therapy, Read at the Annual Meeting, April 24–28, 1950

In the past several years, particularly during the administrations of Dr. Howard W. Bosworth, Dr. H. Corwin Hinshaw, and Dr. Kirby S. Howlett, important reorganization and remarkable expansion of the activities of the American Trudeau Society have taken place. This has been true especially with regard to medical research, including the establishment of teaching and research fellowships. Under the able direction of Dr. Esmond R. Long there has been progressive expansion of the entire medical research program. Because of the importance of this phase of the work, in the future the Society may wish to consider presentation to the Council and possibly to the Business Session of the Society of the reports of the subcommittees of the Committee on Medical Research and Therapy by the individual chairmen.

The Committee on Medical Research and Therapy has held two meetings during the year. The first session was held in New York on November 18, 1949. It consisted of two sessions. The first was a joint session, with investigators receiving grants from the National Tuberculosis Association. Twenty-five investigators reported on their projects, and there was lively discussion of the research being carried out. The joint sessions have proved most valuable and offer an opportunity for the Committee to be brought up to date on the progress of the research program of the Association and afford the investigators a chance to discuss with other workers problems of mutual interest.

An executive session of the Committee was also held on November 18, 1949 at which time the chairmen of the subcommittees presented their reports, consideration was given to applications for grants and fellowships, and a medical research budget was drafted for the fiscal year 1950–1951. In addition, other pertinent matters were considered.

The second meeting of the Committee on Medical Research and Therapy and certain of its subcommittees was held on April 22, 1950 in Washington, D. C. The following summary report is of the parent committee and its subcommittees:

Committee on Medical Research and Therapy

For the fiscal year 1950–1951, 20 renewal grants and 6 new grants amounting to $137,069 were recommended by the Committee. Subsequently this budget was approved by the Board of Directors of the National Tuberculosis Association, and an additional $10,000 was made available for activation of new projects which might come to the attention of the Committee during the year. At its meeting on April 22, 1950, the Committee gave consideration to applications for grants-in-aid received since November 1949. Six such grants were recommended for activation at a total cost of $18,805, the difference between that sum and the addition granted by the National Tuberculosis Association Board of Directors to be covered by savings from last year's budget and anticipated further contributions from the state and local affiliates. In addition, it was voted to recommend that a renewal contribution of $500 be made to the National Society for Medical Research. Two California research projects, financed entirely by the California Association, were endorsed by the Committee. Eight applications for research grants were not approved.

It is especially gratifying to report that from April 1, 1947 to April 1, 1950 contributions for research from affiliated associations of the National Tuberculosis Association have amounted to approximately $160,000. An accounting of these funds has been presented to the Council and Business Session from time to time in previous reports of the Committee. The National Association has continued to contribute at least $100,000 to the Medical Research budget (for the fiscal year 1949–1950 it allocated $112,000). The balance of the budget is made up from the Medical Research Fund, consisting mainly of contributions from affiliated associations. The Council will be interested to know that several state tuberculosis associations have already begun to contribute one per cent of their Christmas Seal funds on a voluntary basis.

The Fellowship Board

The Fellowship Board, under the chairmanship of Doctor Riggins, held two meetings during the year. At the first meeting, held on November 17, 1949, four renewals and one six-month fellowship were approved. In addition, two undergraduate fellowships for study with Dr. Guy Youmans at Northwestern University and Dr. Stuart Mudd at the University of Pennsylvania, respectively, were recommended, in accordance with a previous recommendation of the Laboratory Subcommittee for establishment of fellowships in laboratory research. The Fellowship Board recommended also that two fellowships be established in cooperation with the Division of Medical Sciences of the National Research Council on a basis comparable to fellowships administrated by the Council for other agencies, such as the National Foundation for Infantile Paralysis and the American Cancer Society. One unallocated fellowship was recommended for activation during the year, pending selection of a qualified candidate. The total cost of the fellowships recommended by the Board at its November meeting, and subsequently approved by the Board of Directors of the National Association, amounted to $23,000 for one year.

In accordance with the recommendation of the Subcommittee on Medical Schools and Hospitals, the Fellowship Board recommended at its November meeting that $26,000 be added to the budget for 1950–1951, provided funds were available, for establishment of 10 teaching-resident fellowships. These fellowships would be on a financial basis comparable to Public Health Service fellowships in this category, to be awarded to promising residents in internal medicine who wish to spend one year of their residency in study, teaching, and clinical research in diseases of the chest. The Fellowship Board recommended also that other sources of funds be explored, viz., state and local tuberculosis associations. In addition, it recommended that affiliated associations be requested to consider continuation of certain teaching-resident fellowships, from the financial point of view, originally established with funds from the National Association, provided continuation of the applicant's training is desirable. Subsequently the Board of Directors approved a sum of $20,000 for teaching-resident fellowships for the fiscal year 1950–1951.

At its meeting on April 22, 1950, the Fellowship Board considered new applications and voted to recommend that two teaching-resident fellowships of $2,600 each be activated. The first such fellowship awarded was to Dr. Oscar Ellison of Freedmen's Hospital, Washington, D. C., who has elected to spend a year of residency training under Dr. C. F. Wilkinson at New York University. The second is for Dr. A. Winifred Phillips, now at Stony Wold Sanatorium, New York, who wishes to work for one year in the Bellevue Hospital Chest Service under Dr. J. Burns Amberson. The Fellowship Board recommended that the remainder of funds for teaching-resident fellowships be subject to use for prospective candidates during the year. It also recommended that the Director and the Chairman of the Committee on Medical Research and Therapy be given power to act

for the Board, that the Director consult with the Chairman of the Subcommittee on Medical Schools and Hospitals with respect to selection of qualified candidates, and that he obtain the names of suitable applicants from the heads of certain departments in teaching centers. Proper publicity for the teaching-resident fellowship program, through the BULLETIN of the National Tuberculosis Association, THE AMERICAN REVIEW OF TUBERCULOSIS, and through other channels, was left in the hands of the Chairman of the Committee and the Director of Medical Research and Therapy.

The Clinical Subcommittee

The Clinical Subcommittee, under the chairmanship of Dr. William B. Tucker, held two meetings: one on November 17, 1949 in New York City, and one on April 20, 1950 in St. Louis.

The major activities of this subcommittee for the year were as follows:

1. Preparation of a statement on the "Current Status of Drug Therapy in Tuberculosis," which appeared in the March issue of THE AMERICAN REVIEW OF TUBERCULOSIS (1950, *61*, 436).
2. Consideration of the following projects:
   a) A retrospective study of the therapy of pulmonary tuberculosis
   b) The sponsoring of regional interstate conferences similar to those held at Pembine, Wisconsin
   c) A study of the problem of sudden or accidental death during the administration of pneumoperitoneum
   d) A study of the comparative therapeutic efficacy and toxicity of streptomycin and dihydrostreptomycin sulfate.

The Clinical Subcommittee recommended that these projects be given further consideration by the incoming Clinical Subcommittee if the projects were approved by the parent Committee. The parent Committee approved, in principle, further consideration of items a, b, and d, as recommended by the subcommittee, but disapproved the recommendation in item c.

The Laboratory Subcommittee

The Laboratory Subcommittee, under the chairmanship of Dr. Martin Cummings, met on November 17, 1949 in New York City, and on April 22, 1950 in Washington, D. C.

The major emphasis of this subcommittee was placed on the laboratory aspects of the chemotherapy of tuberculosis and on newer diagnostic methods and procedures.

It was the consensus that para-aminosalicylic acid in combination with streptomycin or dihydrostreptomycin appears to delay the emergence of streptomycin- or dihydrostreptomycin-resistant tubercle bacilli. Laboratory observations concerning neomycin were summarized as follows:

1. Tubercle bacilli become resistant to neomycin *in vitro*.
2. Neomycin is effective against streptomycin- and dihydrostreptomycin-resistant strains of tubercle bacilli *in vitro* and *in vivo*.
3. Preliminary animal protection tests indicate neomycin is not as effective as streptomycin against experimental tuberculosis in animals.
4. Neomycin is not effective against animals infected with neomycin-resistant organisms.

The subcommittee made the following recommendations with regard to the thiosemicarbazones:

1. That investigations now being conducted to determine the toxic and pharmacologic properties of these compounds both in animals and in humans be continued.
2. That methods to determine the sensitivity of tubercle bacilli to the thiosemicarbazones be perfected, since, as yet, no basic bacteriologic information concerning sensitivity studies is available. Methods of determining blood levels of these drugs are available.

The subcommittee believes that evidence presently available is not sufficient to determine the usefulness and reliability of the hemagglutination test, either as a diagnostic aid or as a measure of determining tuberculous sensitivity. The test is promising, however, and warrants further study.

The subcommittee is of the opinion that it is too early to draw definite conclusions concerning the laboratory aspects of the treatment of tuberculosis with terramycin, mycomycin, and viomycin.

The subcommittee recommends that the report of the previous Laboratory Subcommittee dealing with streptomycin sensitivity tests be considered for publication in Diagnostic Standards or, preferably, as a separate report to appear in THE AMERICAN REVIEW OF TUBERCULOSIS.

The Subcommittee on Immunology

During the year the Subcommittee on Immunology, under the chairmanship of Dr. E. P. K. Fenger, held one meeting in New York City, viz., on November 17, 1949.

Progress reports on BCG studies by the Public Health Service were presented to the Committee by Dr. Robert J. Anderson, Chief of the Division of Tuberculosis, and a report on Canadian studies was given by Dr. Robert G. Ferguson.

"Minimum Requirements of BCG Vaccine," prepared by the Division of Biologics Control of the Public Health Service, was reviewed by all of the subcommittees and the parent committee and the suggested revisions were forwarded to the Division by Dr. H. McLeod Riggins, Chairman of the Committee on Medical Research and Therapy.

The committee voted to recommend that the Committee on Medical Research and Therapy consider establishment of a high priority for the promotion and development of a stable dried BCG vaccine which would meet certain minimum requirements, and that laboratory and clinical research in this field be expanded in cooperation with the U. S. Public Health Service.

Dr. E. P. K. Fenger, Chairman of the subcommittee, collected the following information from the three laboratories producing BCG vaccine on the amount of BCG vaccine distributed during the past year.

Dr. Joseph D. Aronson of The Henry Phipps Institute, Philadelphia, stated that with few exceptions the Institute does not provide BCG vaccine outside the state of Pennsylvania. It has, however, provided BCG vaccine to the United States Indian Service. From July 1, 1949 to January 28, 1950, 3,438 persons have been vaccinated in the state of Pennsylvania with its vaccine.

Dr. Konrad Birkhaug of the Health Department of the state of New York stated that the Health Department cannot provide BCG vaccine outside the state of New York except for a few specified Public Health Service projects. It has provided the Philippine Islands with 2,000 doses of vaccine weekly for thirty-eight weeks and a Puerto Rico project with 10,000 doses weekly for twenty-four weeks. During 1948 and 1949, 6,596 vaccinations were performed in New York State.

Dr. Sol Rosenthal of the Tice Laboratories, Chicago, Illinois, reported that during the

year the Tice Laboratories supplied BCG vaccine to 103 institutions. The recipients are located in 16 states, 2 territories, and the District of Columbia. During the year 350 shipments, sufficient to vaccinate 168,272 individuals, were made by the Tice Laboratories.

The Subcommittee on Pulmonary Function Tests

The Subcommittee on Pulmonary Function Tests, under the chairmanship of Dr. Herbert C. Maier, held one meeting during the year, viz., on November 17, 1949 in New York City. The major activity of the subcommittee was the formulation of recommendations on pulmonary function tests for tuberculosis hospitals and sanatoriums. The committee pointed out that the more important laboratory tests for pulmonary function are the following:

1. Determination of pulmonary volumina
   a) Vital capacity
   b) Residual air
2. Maximum breathing capacity
3. Exercise tests
4. Bronchospirometry
5. Gas analyses.

The subcommittee considers the following to be the *minimum* requirements in evaluating pulmonary function:

1. A careful analysis of the history and findings on complete physical examination
2. A fluoroscopic examination which attempts to evaluate the magnitude, speed, and distribution of pulmonary ventilation
3. Evaluation of inspiratory and expiratory chest roentgenograms
4. Determination of the maximum breathing capacity

These tests can be performed in any hospital or sanatorium dealing with diseases of the chest and will yield sufficient information for the management of the great majority of cases.

Doctor Long reports that research projects in progress, or contemplated for the next fiscal year under the auspices of the Committee on Medical Research and Therapy and aided by grants from the National Tuberculosis Association, lie in the following fields:

1. *Chemistry of tubercle bacilli:* Studies are now in progress on the lipids, carbohydrates, and proteins of tubercle bacilli and of the culture medium after growth of bacilli.

2. *Bacteriology:* Projects include development of improved culture media, maintenance of standard strains of bacilli, methods for measuring drug resistance of bacilli, and important studies on the genetics of tubercle bacilli in relation to drug resistance and virulence.

3. *Pathology, immunology, and pathogenesis of tuberculosis:* Studies are in progress on native and acquired resistance to tuberculosis, factors responsible for caseation, liquefaction, and bronchogenic spread of the disease, the sensitizing effects of various fractions of the tubercle bacillus, changes in the blood in tuberculosis, and the problem of calcification in tuberculosis and other diseases.

4. *Clinical research:* Studies in this field include chemotherapy of tuberculosis, comparison of the effects of bed rest and other forms of treatment, and the measurement of pulmonary function, including changes in function with collapse therapy.

Geographic Allocation of Research Grants and Fellowships

Doctor Long also informs us that a total of thirty-six research projects and sixteen research fellowships were approved for the fiscal years 1949–1950 and 1950–1951. The

fifty-two sponsored investigations thus comprised are distributed in nineteen states and the District of Columbia as follows: Maine, 1; Massachusetts, 1; Connecticut, 3; New York, 11; Pennsylvania, 7; Maryland, 3; District of Columbia, 3; Virginia, 1; North Carolina, 3; Georgia, 1; Tennessee, 1; Texas, 1; Indiana, 2; Illinois, 2; Iowa, 1; Wisconsin, 1; Minnesota, 1; Colorado, 2; Washington, 1; California, 6. On a regional basis, these may be grouped as follows: East Coast, 29; South, 7; Middle West, 7; West and West Coast, 9.

In addition to the above are two fellowships to be administered by the National Research Council. Geographic location of these must await selection of qualified candidates.

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

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CLINICAL STUDIES, TUBERCULOSIS

Treatment of Cavities.—The aim of this study has been to compare the results obtained by thoracoplasty with those obtained by extrapleural pneumothorax. Among the 944 patients included, 588 were male and 406 female. Extrapleural pneumothorax alone was performed in 539 patients while thoracoplasty alone was done on 373 patients. The majority of the thoracoplasties were performed in two or three stages. Apicolysis, either extrapleurally or extrafascially, with removal of the transverse processes was done in nearly half of the cases. Extrapleural pneumothorax was performed to obtain selective collapse. When the cavitation was exclusively in the upper lobe, this was separated from the lower lobe in the interlobar space in more than 100 instances. By this technique, sound lung was spared. In a large series of cases, the newly created extrapleural space was filled with a one per cent solution of sodium citrate which was gradually withdrawn and replaced with air. High positive pressures (to plus 30 cm. or more of water) were used to maintain the extrapleural pneumothorax space. This technique as a rule resulted in clear extrapleural cavities with little or no fibrin and few clots, but caused excessive bleeding in many cases. The substitution of sodium chloride solution with penicillin was more satisfactory, but fibrin and clots in the extrapleural space were more troublesome. Extrapleural pneumothorax refills were usually maintained for at least three years. Extrapleural pneumothorax has been the procedure of choice in the operative collapse therapy of pulmonary tuberculosis; thoracoplasty is preferred when a large cavity near the surface of the lung increases the risk of bronchopleural fistula. Thoracoplasty is also indicated when a high degree of fibrotic contraction exists. Finally, geographic considerations may make thoracoplasty preferable to extrapleural pneumothorax. In patients requiring bilateral operative collapse therapy, better late results with far less risk have been obtained with extrapleural pneumothorax. The late results among the bad and desperate risk cases have also been better and the mortality much lower after extrapleural pneumothorax. Among the favorable and satisfactory risk cases, the healing of cavities and the number of patients becoming abacillary have been nearly identical for the thoracoplasty and extrapleural pneumothorax patients; the operative risk has been about the same. Nevertheless, in the great majority of cases extrapleural pneumothorax is preferred since it is less radical, the bony chest wall is saved, and no deformity results. The risk of a residual cavity is less and the collapse of the diseased lung is better than that obtained with the average thoracoplasty; as a rule, it can be made more selective. Extrapleural pneumothorax is to some extent reversible, which is an advantage in the event of a contralateral relapse. The chief disadvantages of extrapleural pneumothorax are the risk of bronchopleural fistulae, a serious and usually fatal complication, and the development of tuberculous empyemata. The most frequent pulmonary complication in the operative treatment of pulmonary tuberculosis is the exacerbation of tuberculous foci which were present before treatment. Bronchogenic dissemination is also frequent. Such pulmonary complications were more frequent after thoracoplasty (17.1 per cent) than after extra-

pleural pneumonolysis (7.5 per cent). Moreover, the pulmonary complications have been more malignant, with a relatively greater mortality, after thoracoplasty. The incidence of tuberculous empyemata following extrapleural pneumothorax was 12.1 per cent while bronchopleural fistulae complicating extrapleural pneumothorax occurred in 4.7 per cent of the cases. It is of interest that, in 630 attempts to perform an extrapleural pneumonolysis, the procedure was not possible in 21 instances, in 19 cases because of adhesions and in 2 cases because of bleeding.—*On treatment of tuberculous cavities by extrapleural pneumothorax and thoracoplasty, M. Seip, Acta tuberc. Scandinav., 1949, Supplement, 19.*—(*K. T. Bird*)

Phrenic Crush and Pneumoperitoneum.—The mechanical effects of unilateral phrenic paralysis supplemented by pneumoperitoneum were studied roentgenographically in 80 cases. In 40 patients with left phrenic paralysis, study of the left side showed an average diaphragmatic rise of 8.1 cm. and an average reduction in the apical-basal (a-b) diameter of 33 per cent. On the right, there was an average rise of 2.6 cm. and an average reduction of 11.1 per cent. There was an average mediastinal shift to the right of 1.5 cm. With right phrenic paralysis, study of the right side showed an average rise of 7.7 cm. and an average reduction of 33.2 per cent. On the left, there was an average rise of 2.4 cm. and an average reduction of 9.4 per cent. There was an average mediastinal shift to the left of 1.6 cm. The mediastinal shift may include a tracheal shift. There may also be cardiac rotation, especially with a left phrenic crush. The effect on the diseased lung is mechanically superior, combined with phrenic crush and pneumoperitoneum, as compared to phrenic paralysis alone. The effect of pneumoperitoneum alone on the unparalyzed side is much inferior to that of phrenic paralysis. The mediastinal shift and reduction of the a-b diameter on the unparalyzed side are both collapse measures for the "good" lung. The extent of diaphragmatic elevation is unaffected by the condition of the pleura.—*Apico-basal diameters of the lungs and mediastinal shift in phrenic nerve crush and pneumoperitoneum therapy, W. Fox, Thorax, June, 1950, 5:* 183.—(*A. G. Cohen*)

Phrenic Crush and Pneumoperitoneum.—As has been noted in a previous article, phrenic crush and pneumoperitoneum result in a shift of the mediastinum away from the paralyzed side. This causes an increase in the side-to-side dimensions of the lung on the paralyzed side. There is also a compensatory motion on that side. These phenomena are not particularly beneficial and help to explain the unpredictable results of these procedures. Conversely, the narrowed side-to-side dimension on the unparalyzed side is a form of collapse therapy for the lesions on that side.—*A modified conception of phrenic nerve crush and pneumoperitoneum therapy, W. Fox, Thorax, June, 1950, 5: 194.*—(*A. G. Cohen*)

Pneumothorax for Tuberculosis.—Eight cases are reported of recurrent nontuberculous spontaneous pneumothorax appearing as a complication of artificial pneumothorax for tuberculosis. There were no effusions. In some cases tension developed. The etiology is believed to be similar to that of cases of spontaneous pneumothorax in otherwise healthy individuals, viz., ruptured emphysematous blebs, et cetera. Thoracoscopy should be performed. Usually it is necessary to discontinue the pneumothorax and select other forms of treatment for the tuberculosis. Therefore, pleurodesis is rarely indicated.—*Recurrent nontuberculous spontaneous pneumothorax. A complication of artificial pneumothorax therapy of pulmonary tuberculosis, M. B. Paul, Brit. J. Tuberc., April, 1950, 14: 44.*—(*A. G. Cohen*)

Spontaneous Cavity Closure.—The rate of spontaneous cavity closure was studied in 790 men selected from 3,000 treated in an Italian high-altitude sanatorium. The group under study included patients with old or recent cavities, in good or poor general condition. In all, pneumothorax could not be instituted;

no surgical treatment was planned, or there was some contraindication to any kind of surgical treatment. There was clinical and bacteriological evidence of cavity closure, confirmed by a standard chest film, in 39 cases. Tomographic examination showed, however, small residual cavities on one or, at most, on 2 sections in 30 cases. In the remaining 9 cases there was no evidence of cavitation on tomographic examination. In 24 cases the reduction in the size of the cavity was more rapid at the beginning and slower as the size of the cavity was reduced by two-thirds. In 5 cases the cavity disappeared within a few weeks and in 10 cases the rhythm of cavity closure did not follow a definite pattern. In 7 cases of recent cavities the diminution of the clinical signs, the conversion of the sputum, and the radiographic clearance occurred in three to fifteen months. In 23 cases of older cavities the healing process took considerably longer. True cavity closure, confirmed by tomographic examination, occurred, therefore, in a little over one per cent of the cases under study. This discrepancy between this low rate, confirmed also by post-mortem studies, and much higher rates reported by others, may be due to the lack of tomographic control.—*La guarigione spontanea delle caverne tubercolari: Meccanismo e frequenza, V. Baroni & L. Vallegiani, Arch. "E. Maragliano" pat. e clin., September–October, 1949, 4: 985.*—(*L. Molnar*)

Eyegrounds in Pulmonary Tuberculosis.—Systematic ophthalmoscopic examination of 591 tuberculous individuals revealed 31 cases (5.2 per cent) of definitely tuberculous lesions and 20 additional instances where such lesions could be suspected. The highest incidence was in a group of 20 patients with typical miliary tuberculosis, 10 of whom had ocular lesions. Among 90 patients with pulmonary tuberculosis and extrapulmonary lesions, 9 ocular cases were found; 11 cases were noted in a group of 270 patients with hematogenous lesions and only one in a group of 211 patients with pulmonary tuberculosis alone. The lesion most frequently found was a solitary tubercle or conglomerate tubercles of the choroid; in one patient scleral lesion was present, in another a tuberculous ulcer of the tarsal conjunctiva, and in 2 others, exudative retinitis were found. Fundal examination is important because the ocular lesions reproduce the evolution of tuberculous lesions in organs inaccessible to direct observation; it is also important in the streptomycin treatment of meningitis as a control of the results; finally, it may be important in the differential diagnosis of nodular lung lesions such as carcinomatosis, stasis, and silicosis.—*Primeros resultados de la investigacion seriada de fondo de ojo en los tuberculosos pulmonares, J. A. Renedo & R. Renedo, Rev. españ. de tuberc., November, 1949, No. 176: 763.*—(*L. Molnar*)

Pelvic Tuberculosis in the Female.—A ten-year study yielded 22 women, varying in age from fourteen to forty years, with pelvic tuberculosis. With 9,717 admissions to the gynecological service, these 22 cases gave an incidence of 0.23 per cent. One-fourth of the patients in the present series had tuberculous lesions demonstrable in the chest roentgenograms. Genital tuberculosis involved the pelvic organs in the following order: Fallopian tubes, 90 per cent; ovaries, 30 per cent; cervix, 5 per cent; vagina and vulva, 0.5 per cent. It is a descending infection, usually spreading downward from the Fallopian tubes. The origin of the pelvic tuberculosis usually is the lungs or the intestines. Hematogenous seeding from a pulmonary focus can implant tubercle bacilli which may remain dormant for varying periods. Bacilli may also enter the pelvic organs by direct extension from the intestines or the mesenteric nodes. The diagnosis of pelvic tuberculosis is suggested by persistent lower abdominal pain and tenderness accompanied by low-grade fever which does not respond to the ordinary treatment of pelvic inflammatory disease of gonorrheal or postabortal origin. There may be loss of weight, anemia, menstrual disturbances, or vaginal discharge. Treatment of pelvic tuberculosis is surgical and should be as radical as good surgical judgment dictates. The presence of an active focus, especially in the lungs, will very often pre-

clude surgical intervention, however. Every case should be given the benefit of a course of streptomycin therapy.—*Pelvic tuberculosis in the female, P. M. Murray, J. Nat. M. A., May, 1950, 42: 147.*—(*L. Hyde*)

Tuberculous Pericarditis.—Tuberculous pericarditis was highly probable but not proved in a patient with far advanced pulmonary tuberculosis, cavitation, left phrenic crush, and pneumoperitoneum. The lesion responded satisfactorily to streptomycin. There were two episodes of pericarditis with effusion seemingly following pneumoperitoneum refills. On both occasions during streptomycin therapy the temperature returned to normal within twelve to eighteen hours and there was marked improvement clinically and roentgenographically within seven days. On the first occasion the sedimentation rate had become normal on the eighth day.—*Tuberculous pericarditis treated with streptomycin, N. Lewin & A. Aronoff, Canad. M. A. J., July, 1950,* **63:** *70.*—(*T. H. Noehren*)

Tuberculoma of the Diaphragm.—Up to 1941 only 16 instances of benign or malignant primary tumor of the diaphragm had been recorded in the literature. A localized diaphragmatic growth can be clearly demonstrated on roentgen examination in almost every case, and usually there is scarcely any difficulty in its detection. In the case presented, a decisive, etiologic diagnosis was not possible in spite of the extensive studies because of the rarity of such a tuberculous lesion, the absence of distinctive symptoms or signs of the disease, and the nonexistence of associated lesions of a similar nature elsewhere in the body. Changes in the right hilar region gave some hint as to the possibility of an inflammatory lesion. Kymography and diagnostic pneumoperitoneum clearly delineated the lesion to be embedded in the diaphragm. This conclusion was verified by operation, and the diagnosis of a tuberculoma was thus settled. —*Tuberculoma of the diaphragm, C. L. Tu & C. K. Hsieh, Am. J. Roentgenol., June, 1950, 63: 822.*—(*T. H. Noehren*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

ACTH for Beryllium Granulomatosis.—Since beryllium granulomatosis is characterized by excessive fibrous tissue and cellular reaction in the interalveolar septae and occasionally by hyperglobulinemia, an alteration of the disease process with the adrenocorticotropic hormone (ACTH) was postulated. On that basis, a 27-year-old employee of a fluorescent lamp plant for two and one-half years, with symptoms and roentgenographic findings suggestive of the disease, was given ACTH, 25 mg., 4 times a day for twenty-eight days. Increased aggressiveness and emotional instability finally necessitated discontinuance of the hormone. A striking improvement occurred as evidenced by the clinical response and improvement in roentgenograms and respiratory function studies. The response of this patient to ACTH demonstrated a temporary improvement and suggests that this disease is reversible. Regressions such as were demonstrated in this patient are regarded by the authors as unlikely to occur spontaneously.—*The effect of adrenocorticotropic hormone (ACTH) on beryllium granulomatosis, B. J. Kennedy, J. A. P. Pare, K. K. Pump, & R. L. Stanford, Canad. M. A. J., May, 1950, 62: 426.*—(*T. H. Noehren*)

Tuberculin Response in Sarcoid.—In order to clarify the absent or reduced ability to react to tuberculin, 71 proved cases of Boeck's sarcoid with skin manifestations were studied. The diagnosis was made in all cases on the basis of microscopic examination of skin biopsy and was supported by associated manifestations of the disease. Tuberculosis was eliminated by numerous cultures and animal inoculations. These 71 patients were tested with Pirquet's reaction (2 scratches) and with tuberculin, 0.1 mg., intracutaneously. Negative patients were further tested with tuberculin, 1 mg., and eventually with 10 mg. Positive tuberculin reactions were found in 21 (29.6 per cent) while in the other 50 patients no positive reaction was demonstrated; 14 of these were not tested with doses larger than

0.1 mg. Only 6 of the patients were under thirty years of age and 72 per cent were over forty when examined. Thus, even after the age of forty, two-thirds of the sarcoid patients were tuberculin negative. Since 90 to 100 per cent of the Norwegian population after the age of forty years is tuberculin positive, this large number of tuberculin-negative sarcoid patients can hardly be explained on the grounds that they have escaped a primary tuberculous infection. Eleven (22 per cent) of the tuberculin-negative sarcoid patients had radiologically demonstrable calcium deposits in the lungs or at the hilus. This also makes it improbable that the high frequency of negative tuberculin reactions in sarcoid patients is due to the fact that they have escaped tuberculous infection. The frequency of negative reactions must be due to the sarcoid disease itself. The absent or weak tuberculin sensitivity is assumed to be due to a hitherto unknown chronic infection which causes an increased resistance to tuberculosis. Such resistance not only cures an original tuberculous infection, but is also able to prevent reinfection.—*Tuberculin sensitivity in Boeck's sarcoid, R. Th. Bjørnstad, Acta tuberc. Scandinav., 1950, 24: 15.*—(*K. T. Bird*)

Splenic Sarcoidosis.—In 4 cases of marked splenomegaly due to Boeck's sarcoid, the diagnosis was not made before pathologic examination. The spleen is the second most common site of involvement in the course of generalized sarcoidosis. When the spleen is enlarged and other findings are insignificant, however, Banti's disease or tuberculosis is usually diagnosed. The 2 white women, one Negro woman, and one Negro man in the group presented marked splenomegaly as the predominant physical finding associated with weight loss, weakness, and various gastrointestinal complaints. The spleen was removed from all of the patients and a specimen of the liver was obtained from 2 of them. There were no deaths and one patient was alive 23 years after her operation. So far as could be determined, lesions were predominantly limited to the spleen, although 3 patients had changes in the liver. No bone lesions were seen on roentgenographic examination and only one patient had lung lesions suggestive of sarcoidosis. Pathologically, the spleens were similar except that one contained coarse nodules reminiscent of nodular cirrhosis of the liver. Microscopically these nodules were confluent tubercular lesions in uninvolved splenic tissue. The other spleens showed practically complete replacement of normal tissue by fairly discrete sarcoid tubercles, each representing a circumscribed entity. "Asteroid bodies" or similar inclusions were found within giant cells in all 4 spleens. Sarcoid lesions occur almost exclusively in the spleen frequently enough to merit the consideration of sarcoidosis in the differential diagnosis of splenomegaly.—*Sarcoidosis of the spleen: Report of four cases with a twenty-three year follow-up in one case, S. Kay, Am. J. Path., May, 1950, 26: 427.*—(*J. S. Woolley*)

Liver Biopsy in Sarcoidosis.—Three cases are presented in which the diagnosis of sarcoidosis was confirmed by liver biopsy. Laboratory evidence of liver disease was present in only one of these cases. This test may be of considerable importance in the sarcoid patient in whom, because of the absence of cutaneous lesions or of superficial lymphadenopathy, histologic studies are otherwise impossible. It is suggested that in patients with otherwise unexplained hilar lymphadenopathy needle biopsy of the liver may be a valuable approach.—*Liver biopsy in sarcoidosis, M. M. Baird, A. Bogoch, & J. B. Fenwick, Canad. M. A. J., June, 1950, 62: 562.*—(*T. H. Noehren*)

Contraindications to Air Travel.—Air travel should not be attempted by persons with active pulmonary tuberculosis nor by those with hemoptyses even though their tuberculosis is fibroid and quiescent. Patients with uncomplicated pneumothorax may in certain cases be allowed to fly at low altitudes. Acute pneumonias and pleurisies are absolute contraindications. Emphysema is a relative contraindication; each case must be studied care-

fully. In asthma, caution must be observed. Occasionally asthmatics with severe symptoms have made plane flights against advice and one of the author's patients was apparently benefited by the experience. Another with a lung cyst survived a series of aerial acrobatics. Atelectasis is a relative contraindication depending upon its extent and location and the result of airplane travel may be difficult to predict. Bronchiectasis does not constitute a contraindication unless the lesion is large or accompanied by acute inflammation. Tumors are not contraindications if they do not interfere with normal respiration. The situation is different if there is marked compression of the lung, bronchial stenosis, or metastasis of a malignant growth. After thoracoplasty in which not more than 5 ribs have been removed and respiratory function has not been compromised, successful flights have been made without harm to the patient. Pneumonectomy may be considered an absolute contraindication. Some patients who have had lobectomies may be allowed to fly under suitable conditions. Airplane flights have been used as a treatment for whooping cough and the effects have been satisfactory in some cases.—*Possibilités et contre-indications du vol en avion chez les malades atteints d'affections broncho-pleuro-pulmonaires, P. Weiller, Le Poumon, March-April, 1950, 6: 113.*—(*A. T. Laird*)

Lung Changes from Nitric Oxide.—This is a report of 4 cases of acute intoxication from nitric oxide with pulmonary changes, one of which was complicated by pulmonary edema and terminated by death. Similar cases were observed by other Italian authors during the recent war. Owing to the shortage of copper sulfate, Italian wine growers prepared it themselves. They had no adequate protection from the harmful effects of the fumes of nitric oxide and its derivatives which were given off in the process. The clinical course of the 3 patients who survived was very similar and was characterized by transitory malaise, burning in the throat, dyspnea, and dry cough immediately after breathing the gas. After an asymptomatic period of a few days to a few weeks, cough, dyspnea, chest pain, fever, and perspiration appeared. The cough, dry at first, became productive later, often with blood-streaking or frank hemoptysis. The patient usually sought medical advice because of this latter symptom. The physical examination of the chest was of little help in the diagnosis. The blood count showed a normal white count with neutropenia and relative lymphocytosis. Radiologic examination of the chest in the cases reported here and in cases described by other Italian authors revealed 3 types of lesions: (*1*) accentuation of the bronchovascular markings, (*2*) miliary dissemination, and (*3*) patchy bronchopneumonic infiltration. It is thought that the accentuation of the bronchovascular markings is due to blockage of the lymphatic circulation, the miliary nodules are the expression of a productive tissue reaction, and the bronchopneumonic infiltration corresponds to exudative lesions. Breathing nitric oxide in low concentrations over a long period appeared to cause the nodular reaction, while inhaling large quantities of the gas in a short time seemed to produce the bronchopneumonic pattern. Probably the three types of reaction are different phases of the same process. The fact that many ambulatory cases with long exposure to high concentrations of the gas showed only slight radiologic changes suggests that individuals differ in their resistance to the agent. The diagnosis was based mainly on the occupational history of the patient. With the end of the copper shortage, no new cases were observed.—*Quadri pseudomiliarici nella intossicazione acuta da gas di ipoazotide, G. Rolle, Arch. "E. Maragliano" pat. e clin., March-April, 1948, 3: 539.*—(*L. Molnar*)

Cardiopulmonary Schistosomiasis.—Bilharzic infestation of the lungs ("cardiopulmonary bilharziasis" or "bilharzic cor pulmonale"), secondary to intestinal infestation with *Schistosoma mansoni* or urinary infestation with *Schistosoma haematobium* is not rare in Egypt. Seven cases of cardiopulmonary schistosomiasis are described. Obliterative arteriolitis in the lung is caused by the bilharzia ova. This

causes a rise in pulmonary blood pressure, hypertrophy of the right ventricle, and right-heart failure. The greatest incidence is between 12 and 35 years of age. The disease is more common in men than in women. Symptoms are those of congestive heart failure; hemoptysis, asthma, cyanosis, clubbing, and eosinophilia may occur. Roentgenograms reveal enlargement of the right ventricle and mitral configuration of the heart. Fine mottling may be seen in the lungs. Electrocardiographic changes characteristic of right ventricular strain may appear. Hepatosplenomegaly is present and bilharzia ova may be found in the stool. The following diseases may simulate bilharzic cor pulmonale: (*1*) rheumatic mitral incompetence, (*2*) patent interauricular septum, (*3*) patent ductus arteriosus, (*4*) cardiac type of beri beri. The treatment consists of the administration of antimony which, however, is contraindicated in the presence of cardiac failure.—*The syndrome of cardiopulmonary schistosomiasis (cor pulmonale), M. Radwan Kenawy, Am. Heart J., May, 1960, 39: 678.*—(*G. C. Leiner*)

Acute Cor Pulmonale.—Cor pulmonale may be produced by causes other than pulmonary emboli. It is caused by a sudden increase of the resistance in the pulmonary circulation in patients in whom the right ventricle has been working under increased strain for some time. A 36-year-old Negro woman was observed who died from a bronchogenic carcinoma. There was marked constriction of the left pulmonary artery by annular infiltration of the tumor, atelectasis of most of the left upper lobe, metastases throughout both lungs, and paralysis of the left hemidiaphragm. An electrocardiogram taken twenty-four hours before death was typical of acute cor pulmonale. The second case was that of a 21-year-old white woman with bilateral, far advanced, pulmonary tuberculosis who underwent a two-stage thoracoplasty. After the second stage there was complete collapse of the left upper lobe and splinting of the entire left chest. Pneumonia in the right lower lobe and myocarditis developed. The electrocardiogram taken immediately before death showed the signs of acute cor pulmonale. Some of the electrocardiographic changes of acute cor pulmonale are caused by dilatation of the right ventricle and rotation of the heart, others by myocardial ischemia.—*Acute cor pulmonale in the absence of pulmonary embolism, I. Mack, R. Harris, & L. N. Katz, Am. Heart J., May, 1960, 39: 644.*—(*G. C. Leiner*)

Antihistaminic Drugs for Colds.—Antihistaminic drugs in doses advertised as effective were used without success in the treatment of naturally occurring common colds. When used prophylactically, the drugs were not of value in preventing artifically induced colds in human volunteers.—*The failure of antihistaminic drugs to prevent or cure the common cold and undifferentiated respiratory diseases, A. E. Feller, G. F. Badger, R. G. Hodges, W. S. Jordon, Jr., C. H. Rammelkamp, & J. H. Dingle, New England J. Med., May 11, 1960, 242: 737.*—(*A. G. Cohen*)

Fat Embolism.—Fat embolism has been defined as that condition which occurs when a liquid fat enters the circulating blood and is transported in globules large enough to obstruct the lumen of capillaries, especially in the lungs, kidney, liver, and brain. The clinical picture varies from cases so mild as to pass unnoticed to the rapidly fatal cases. The onset may be sudden but usually there is an asymptomatic period lasting from 3 to 72 hours. Following this, either the picture of pulmonary embolism or cerebral embolism develops, or they may be combined. In the pulmonary type there is a rapid increase in the pulse and respiratory rates. Cyanosis may develop; moist rales are heard in both lung bases due to passive congestion. A productive cough is a usual symptom, and free fat may be found in the sputum. The blood pressure is normal until the terminal stages when the heart fails. Diagnosis is made by the history of injury, the occurrence of pulmonary and/or cerebral symptoms the presence of free fat in sputum and urine, chest roentgenogram showing diffuse haziness and clouding of lung fields, and

the presence of fat emboli in the choroidal vessels. Two precautions must be taken in collecting urine specimens for examination: (*1*) the catheter must not be lubricated with oil; (*2*) all the urine must be obtained, as fat is lighter than urine and rises to the top of the bladder. At post-mortem examination the lungs show areas of congestion, frothy fluid, and small subpleural hemorrhages. Many fat emboli can be stained in small arterioles and capillaries. Treatment is symptomatic, since there are no therapeutic measures specific for fat emboli. Of importance are preventive measures such as careful handling of fractures with early immobilization and the use of a tourniquet in orthopedic operations.—*Fat embolism, E. S. James, Canad. M. A. J., June, 1950, 62: 548.*—(*T. H. Noehren*)

Phrenic Paralysis in Pneumonia.—In 6 cases of pneumonia, homolateral paralysis of the diaphragm appeared coincidentally or shortly afterwards. The paralysis lasted for many weeks and in one case is probably permanent. Two cases were associated with pleural effusion, one with dry pleurisy and two with lung abscess. Toxic or inflammatory diaphragmitis was disfavored as a possibility. It is believed that the paralyses were the result of a toxic or inflammatory neuritis of the phrenic nerve. In one case there was also ipsilateral vocal cord paralysis.—*Unilateral paralysis of the diaphragm and larynx associated with inflammatory lung disease, B. Freedman, Thorax, June, 1950, 5: 169.*—(*A. G. Cohen*)

Stannic Oxide Pneumoconiosis.—Inhalation of stannic oxide for long periods is productive of benign, symptomless pneumoconiosis with no significant pulmonary fibrosis. A case of benign pneumoconiosis due to stannic oxide, in a man aged 72 years, is presented with clinical, autopsy, and analytical findings. The patient had no respiratory symptoms. Vital capacity was 85 per cent of normal. A history was obtained of exposure to dust and fumes from a detinning furnace for a period of eighteen years, this exposure having terminated eighteen years previously. The chest roentgenogram revealed uniform mottling of both lung fields by discrete shadows, with the density of lipiodol droplets, varying in size from less than 1 mm. to about 2 mm., and evenly scattered throughout the lungs, 2 to 4 mm. apart. There was no evidence of enlarged hilar lymph nodes. Tin deposited in the lungs in this form is nontoxic systemically. Analytical and microincineration studies are necessary to differentiate this condition from simple anthracosis. It is considered significant that in 10 of the 11 reported cases of stannic oxide pneumoconiosis the workers had either been furnace tenders or had worked in the furnace room. It is thus likely that exposure to furnace fumes rather than to dust from the finished product is the most important source of this condition.—*Stannic oxide pneumoconiosis, C. C. Dundon & J. P. Hughes, Am. J. Roentgenol., June, 1950, 63: 797.*—(*T. H. Noehren*)

Pneumothorax in Neck Surgery.—In the past five years, 18 cases of pneumothorax and 2 of mediastinal emphysema were encountered following operations upon the head and neck. The pneumothorax was bilateral in 12, homolateral in 4, and contralateral in 2 cases. Almost every patient showed some variation in the normal respiratory pattern during the operation, usually during the second half of the procedure. There were 2 deaths. The pleural apex was opened in only one case. In every case, the middle layer of the deep cervical fascia was opened. This is believed to have resulted in a tension mediastinal emphysema which in turn resulted in a pneumothorax. It is not believed that the complication was the result of alveolar rupture secondary to obstructive emphysema. Prompt underwater catheter drainage was the preferred treatment.—*Pneumothorax and mediastinal emphysema complicating neck surgery, L. Bowden & O. Schweizer, Surg., Gynec. & Obst., July, 1950, 91: 81.*—(*A. G. Cohen*)

Cytology of Bronchial Carcinoma.—Early diagnosis of bronchial carcinoma may be made

by the cytological examination of secretion obtained from the suspected mass or from the bronchus nearest to it. A little material, often containing tissue particles, may be aspirated through a bronchial catheter introduced into the affected bronchus under fluoroscopic control. The material thus obtained is fresh and in sufficient concentration for microscopic examination. The procedure is facilitated by using a urethral catheter with a metallic guide in it. The size of the catheter must be chosen according to the bronchus to be aspirated. The aspirated material is examined with the Pappenheim and Papanicolaou methods. Twenty-two cases of suspected tumor were examined: typical tumor cells were found in 17 and suspicious tumor cells in 2 cases. In 7 cases the cytological examination revealed tumors in the early stage without metastases. The aspirated material was obtained in 13 cases from upper lobe lesions, 5 of which were in the early stage. The cytological diagnosis was confirmed in 7 cases by histological examination: Cytological examination of aspirated material is considered as a practical and reliable diagnostic method which compares favorably with such other methods as sputum examination, bronchoscopic aspiration, bronchoscopic biopsy, and bronchography.—*Zytologische Frühdiagnose des Bronchialkarzinoms mit Hilfe der gezielten Bronchialsonde, H. Hengstmann & D. Wittekind, Deutsche med. Wchnschr., January 20, 1950, No. 3: 101.*—(*L. Molnar*)

Carcinoma of Lung.—In 69 cases of bronchogenic carcinoma, bronchoscopic examination showed direct evidence of tumor in 38 per cent and indirect evidence in 17 per cent. Positive biopsies were obtained in only 22 per cent. In the peripheral type of tumor, the differential diagnosis rests between carcinoma and tuberculoma, adenoma, hamartoma, and bronchogenic cyst. Absolute proof of the presence of cancer generally is impossible without surgical exploration. In the lobar or segmental type, the differential diagnosis is between cancer, tuberculosis and abscess. Tuberculosis is determined by the presence of tubercle bacilli in the sputum. As between cancer and abscess, the latter has a more acute onset and course, smoother walls in the roentgenogram, and is more responsive to medical therapy. Cases are presented to illustrate the frequency of carcinoma despite negative bronchoscopic findings. A plea is made for early surgery in cases in which the suspicion of cancer is sufficient.—*Carcinoma of the lung, V. H. Kaunitz, New England J. Med., July 13, 1950, 243: 59.*—(*A. G. Cohen*)

Sputum in Pulmonary Malignancy.—A total of 178 specimens of sputum and bronchial secretions from 110 patients were examined microscopically, without prior knowledge of the clinical history. This included 145 specimens of sputum, 143 of which were examined by smears and 130 by paraffin sections; and 33 bronchial secretions, all of which were examined by the smear technique; paraffin sections as well were made of 16 of the latter. Positive results were obtained in 17 of 20 proved or probable cases of cancer of the lung. In 90 cases apparently without pulmonary tumor, one false positive report was made. In the case of sputum, the smear technique gave a slightly higher yield of positive results than paraffin sections, but it is felt that there are advantages to both methods and that they complement each other (Author's summary).—*The value of sputum examination in diagnosis of cancer of the lung, R. C. Ross, Canad. M. A. J., July, 1950, 63: 11.*—(*T. H. Noehren*)

Bronchogenic Carcinoma.—In a series of 299 cases of bronchogenic carcinoma, there were 5 cases of peripheral neuritis (1.7 per cent). The neuritis dominated the clinical picture at first. There was minimal involvement of the central nervous system. The lesion was a reversible demyelinization. There was a complete lack of correlation with any of the features of the tumor. The relationship between the neuritis and carcinoma was found to be statistically significant but there is no apparent explanation for the relationship.—*The association of bronchial carcinoma and peripheral neuritis, B. Lennox & P. Stobo,*

Quart. J. Med., April, 1950, 19: 97.—(A. G. Cohen)

Leiomyoma of Bronchus.—Leiomyoma of the bronchus is an extremely rare tumor. A case is reported in which the tumor arose in the apical division of a lower lobe bronchus and grew out so as to occlude the main bronchus. A pneumonectomy was performed.—*Leiomyoma of the bronchus, S. I. Turkington, G. A. Scott, & T. B. Smiley, Thorax, June, 1950, 5: 138.—(A. G. Cohen)*

Lung and Mediastinal Cysts.—Seven cases, 6 of which were bronchogenic cysts (2 involving the mediastinum, and 4 involving the lung) are presented. The seventh patient demonstrated cystic dilatation of the bronchi. The diagnosis of 3 of these cases was purely incidental and, of the total, 5 were operated upon and one death was recorded. After each operation a pleural reactioh occurred, necessitating one to 3 aspirations and treatment with penicillin. Two patients complained of pain in the thorax for several months postoperatively accompanied by shortness of breath and weakness in the right arm. In one patient a recurrent laryngeal paralysis disappeared after surgery. The treatment of pulmonary and mediastinal cysts is surgical when the general state of health of the patient is satisfactory.—*Cysts of the lung and of the mediastinum, J. B. Jobin, Canad. M. A. J., July, 1950, 63: 48.—(T. H. Noehren)*

Cystic Hygroma of Mediastinum.—The authors review 7 cases from the literature and add one of their own. The lesion is a multicystic structure, the spaces of which are lined by flattened endothelial cells. It is adherent to neighboring structures. In uncomplicated cases, the spaces contain a thin watery fluid. Hygromata are to be distinguished from so-called spring-water cysts. The age incidence ranges from 2 to 80 years. Symptoms are characteristically absent. The cysts may occupy the inferior or superior mediastinum and usually are placed anteriorly and project towards the right side. Radiographically they cast well-defined, homogeneous shadows which may be rounded, lobulated, or somewhat irregular in outline and vary considerably in size. The preferred treatment is surgical excision.—*Cystic hygroma of the mediastinum, H. R. S. Harley & C. E. Drew, Thorax, June, 1950, 5: 105.—(A. G. Cohen)*

Traumatic Hemothorax.—A total of 400 patients with thoracic injuries was seen. Hemothorax was present in 230 (58 per cent). Final results were: cured, 64; satisfactory, 33; poor, 2.2; and dead, 0.4 per cent. The average duration of illness was 68 days from the time of injury. Infection occurred in 22 per cent, a great improvement over the occurrence in World War I. The incidence of infection was much higher when treatment was late and inadequate. The average duration of illness in adequately treated, uncomplicated, sterile cases was 27.8 days. Traumatic hemopneumothorax occurred in 44 cases. The rate of infection in these cases was higher. Clotted hemothorax occurred in 23 cases, and was twice as frequent with bullet wounds as with those from splintered fragments. Some patients were cured with aspiration, but decortication was necessary in 18 cases. There were 30 cases of organizing hemothorax including organized clotted hemothorax and chronic emphyema. The optimal time for decortication was the fourth week. Earlier operation was more likely to lead to empyema, and late operation was futile. Operation was necessary in 63 cases (27 per cent).—*Final results in traumatic hemothorax, A. G. Ogilvie, Thorax, June, 1950, 5: 116.—(A. G. Cohen)*

Malignant-appearing Lesions.—At present every pulmonary lesion which is relatively atypical in roentgenographic appearance or clinical course must be considered malignant until proved otherwise. A group of 22 cases demonstrates that benign tumors and inflammatory lesions can be differentiated only with great difficulty and sometimes not at all from malignant lesions. Until there are greater refinements in diagnostic methods, there will be need for more exploratory thoracotomies,

lobectomies, and pneumonectomies. An increasing number of benign lesions will be removed because of overlapping characteristics and other diagnostic uncertainties which do not allow any delay in action.—*Chest lesions often confused roentgenographically with primary cancer of the lung, P. C. Swenson & R. H. Leaming, Am. J. Roentgenol., May, 1950, 63: 629.*—(*T. H. Noehren*)

Chest Roentgenograms.—The possibilities and limitations of roentgenography in the diagnosis of chest conditions are emphasized by the relationship of symptoms and the appearance of abnormal shadows in the roentgenogram. Pulmonary edema can be detected before the onset of appreciable symptoms or within a few hours thereafter. It is detectable in the roentgenogram from six to twelve hours before the appearance of physical signs. Pleural effusion in amounts of 100 cc. or more can be detected by making a postero-anterior roentgenogram with the patient lying on the side of the lesion. Bacterial pneumonias produce roentgenographic changes in as short a time as two hours, most frequently within six hours and almost invariably within twelve hours after the onset of symptoms. Atypical or virus pneumonias may give no distinctive roentgen findings for 24 to 48 hours after the onset of symptoms. Acute miliary tuberculosis invariably produces symptoms before the development of roentgenographic signs. The latter may not be present for as long as seven weeks after the onset of symptoms. Nodular lesions such as those produced by metastasis or nodular tuberculosis are demonstrable when their size is 3 mm. or larger in diameter. All pulmonary metastases are roentgenographically visible before the onset of symptoms or physical signs. Bronchogenic carcinoma almost invariably gives positive roentgen signs when symptoms are present.—*Roentgen examination of the chest, L. G. Rigler, J.A.M.A., March 18, 1950, 152: 773.*—(*H. Abeles*)

Pulmonary Artery Enlargement.—Despite the existence of exceptions, the main pulmonary artery and its branches remains the most important differential point of roentgenographic diagnosis between pulmonic stenosis and similar conditions. Eight cases of mild, uncomplicated, pulmonic stenosis and one case of severe pulmonic stenosis, originally complicated by a right-to-left shunt through a septal defect but without an overriding aorta, are analyzed and presented. The most significant roentgenographic finding in 6 of these 9 cases was a poststenotic dilatation of the "main pulmonary artery" which did not extend to include the hilar or intrapulmonary branches. The majority of cases failed to show generalized cardiac or selective chamber enlargement. Left auricular enlargement was not observed in any case.—*Roentgenographic changes in pulmonic stenosis, R. F. Healey, L. Dexter, M. Elkin, & M. C. Sosman, Am. J. Roentgenol., June, 1950, 63: 813.*—(*T. H. Noehren*)

ANTIMICROBIAL THERAPY

Prolongation of PAS Effect.—A new compound, *p*-(di-n-propylsulfamyl)-benzoic acid, 'Benemid,' is described. It is orally effective and capable of producing a twofold enhancement of plasma concentrations of both penicillin and para-aminosalicylic acid (PAS). The drug is readily absorbed from the gastrointestinal tract and gives rise to effective plasma concentrations within two hours. Single 1 and 2 gm. doses of the drug are effective in producing enhancement of plasma concentrations of penicillin and PAS for periods as long as eight hours. Repeated doses of 0.5 gm. and 1 gm. every six hours maintain effective concentrations of the drug, and the slow rate at which the drug is eliminated from the body permits the administration of the drug at intervals spaced as widely as every twelve hours. In the study of more than 50 patients, some of whom have received 1.5 gm. of 'Benemid' daily for as long as forty days, there have been no evidences of toxicity.—*The influence of a new benzoic acid derivative on the metabolism of para-aminosalicylic acid (PAS) and, penicillin, W. P. Boger, J. O. Beatty, F. W. Pitts, & H. F. Flippin, Ann. Int. Med., July, 1950, 33: 18.*—(*T. H. Noehren*)

Tuberculous Meningitis.—The combination of streptomycin and *p*-aminosalicylic acid (PAS) is the most effective treatment for tuberculous meningitis. Of 9 patients treated with combined therapy from the beginning, 8 are alive and well after seven to eleven months, whereas of 17 patients treated with streptomycin alone only 3 are alive at the end of two to three years. If previous treatment with streptomycin has been employed for pulmonary tuberculosis, combined therapy is distinctly less effective. The most successful routine has been: (*1*) Intramuscular streptomycin, 0.5 gm. twice daily, is given for two months, then 0.5 gm. daily for four months. (*2*) Intrathecal streptomycin, 100 mg. daily, is employed for the first week, 50 mg. daily from the second through the fourth week, 50 mg. three times a week for the second month, 50 mg. twice a week for the third month, and 50 mg. once a week for the fourth month. (*3*) PAS, 30 to 40 gm., is given daily by continuous intravenous drip in 2 liters of saline with 2 ampules of heparin. This is carried out for one month. In the second month this therapy is continued if technically possible; if not, PAS, 14 gm., is started orally, and this is continued throughout the third month. Continuation of oral PAS treatment depends on the course of the illness and on the findings in the cerebrospinal fluid. Intrathecal injection of an isotonic solution of 0.3 per cent of PAS buffered to pH 7.4 has been found feasible and may be applicable to streptomycin-resistant cases.—*Resultate der kombinierten Behandlung der Meningitis tuberculosa mit Streptomycin und Paraaminosalicylaure (PAS) im Vergleich zur Behandlung mit Streptomycin allei, W. Loffler & S. Moeschlin, Schweiz. med. Wchnschr., April 15, 1950, 80: 365.*—(*H. Marcus*)

Tuberculous Meningitis.—In a case of tuberculous meningitis treated with streptomycin there was restoration of ability for normal activity. Complicating adhesive arachnoiditis was relieved by surgical intervention on one occasion with good results. However, the patient died 27 months after the original attack of meningitis from reformation of arachnoidal adhesions, internal hydrocephalus, and reactivation of meningeal tuberculosis (Authors' summary).—*Prolonged survival following streptomycin therapy of tuberculous meningitis, H. S. Tacket & G. S. Lovejoy, J.A.M.A., March 4, 1950, 142: 648.*—(*H. Abeles*)

Streptomycin for Tuberculous Meningitis.—Of 33 children with tuberculous meningitis treated with streptomycin alone or in conjunction with "sulfon" or *p*-aminosalicylic acid (PAS), 17 (52 per cent) are dead, 16 (48 per cent) are alive. The prognosis was better in the higher age groups (between eleven and fifteen years) than in the younger children. Early diagnosis and early treatment were essential; the course of the disease was far worse in those patients who were not treated before the third week of the illness. Simultaneous intramuscular and intrathecal administration of streptomycin should be employed over a long period without interruption. The combination of streptomycin and "sulfon" did not give better results than streptomycin alone, but 8 of 12 children treated with streptomycin and PAS were cured. Damage to the labyrinth was detected in 85 per cent of the patients. Adiposity developed in 3 children, possibly due to damage of the diencephalon by streptomycin. Moral insanity developed in 2 children during the streptomycin treatment.—*Zur Streptomycinbehandlung der Meningitis tuberculosa in Kindesalter, E. Lorenz, Wien. klin. Wchnschr., June 16, 1950, 62: 417.*—(*G. C. Leiner*)

Streptomycin Resistance.—It seems probable that strains of tubercle bacilli derived from patients receiving streptomycin treatment may consist of a mixture of organisms of different degrees of sensitivity. An attempt was made to determine the proportion of resistant to sensitive organisms that could appear as resistant in the test. This was done in Tween 80-albumin liquid medium and in the same medium without Tween 80. After seven days incubation the proportions ranged from 1:6 to 1:30; after ten days from 1:37 to 1:2,700; and after fourteen days from 1:440

to 1:80,000. The growth rate of bacilli was greater in medium without Tween than with it.—*The behaviour of mixtures of streptomycin-sensitive and -resistant tubercle bacilli in liquid medium sensitivity test, D. A. Mitchison, Thorax, June, 1950, 5: 162.*—(*A. G. Cohen*)

Streptomycin Resistance.—The sputum from 18 patients with progressive pulmonary tuberculosis during treatment with streptomycin was studied. Weekly specimens, to which various concentrations of streptomycin were added, were inoculated on Herrold's egg-agar medium. Simultaneous cultures were tested for sensitivity in Tween 80-albumin medium. Two groups of cases developed. In one, strains of low resistance appeared soon and persisted. In the other, these strains were gradually replaced by strains of higher resistance. There was evidence that, in some cases, differences in sensitivity appeared in different parts of the lung. There was also evidence of the occasional development of a streptomycin-dependent strain.—*Development of streptomycin resistant strains of tubercle bacilli in pulmonary tuberculosis, D. A. Mitchison, Thorax, June, 1950, 5: 144.*—(*A. G. Cohen*)

Streptomycin for Tuberculous Pleurisy and Peritonitis.—Five cases of tuberculous pleurisy with effusion, 3 cases of tuberculous peritonitis, and one case of both tuberculous pleurisy and peritonitis were treated with streptomycin. The fluids removed from the affected cavities had specific gravities varying between 1.016 and 1.020 and the white cell counts were from 240 to 420 per cu. mm., lymphocytes predominating. No effort was made to recover tubercle bacilli from these fluids because the incidence of success in such attempts would be relatively low. Patients received from 0.5 to 2.0 gm. of streptomycin daily. The total dose of streptomycin given in each case varied from 11 to 50 gm. It was felt that streptomycin materially shortened the febrile course, and no toxic symptoms were observed. The suggested course of therapy for tuberculous pleural effusion was 10 to 20 gm. and for tuberculous peritonitis 30 to 60 gm. It was emphasized that exudative tuberculous pleurisy and peritonitis must be regarded as incident to some intrathoracic and intra-abdominal tuberculous lesions and that these are not affected by the short courses of streptomycin. The underlying lesions must be treated by bed rest and other appropriate measures.—*Streptomycin in the treatment of exudative tuberculous pleurisy and peritonitis, I. K. C. Chu, Chinese M. J., November, 1949, 67: 577.*—(*B. Hyde*)

PAS for Pulmonary Tuberculosis.—Twenty-two cases of advanced pulmonary tuberculosis were treated with para-aminosalicylic acid (PAS). The dosage was 10 to 15 gm. by mouth daily for 30 to 312 days. Five patients had been unaffected by previous streptomycin therapy and 9 had relapsed after it. All had positive sputum. There were few toxic reactions, mostly of a minor nature. At the termination of treatment the sputum was still positive in 13, negative on concentrate but positive on culture in 5, and negative on culture in 3. Fourteen patients improved symptomatically while there was roentgenographic improvement in 12. Bronchial lesions improved in 3 of 4 cases.—*Para-aminosalicylic acid (PAS) in chronic pulmonary tuberculosis, A. S. Dooneief, A. Buchberg, & M. M. Steinbach, New England J. Med., June 1, 1950, 242: 859.*—(*A. G. Cohen*)

Intracavitary Streptomycin Therapy.—Intracavity administration of streptomycin may be effective, especially if associated with other methods, in the treatment of giant cavities when the pleural space is obliterated. The streptomycin was introduced into the cavity through a catheter under fluoroscopic control, in 3 doses of a 25 per cent solution up to a total of 0.75 gm. per day; the same total dose was given in three daily intramuscular injections. The instillation of the drug was preceded by lavage with a buffer solution (35 per cent sodium phosphate) in order to obtain a pH of 8 to 9, which is the optimum for the therapeutic effect of streptomycin. Twenty-three cases were treated with this method and others

are still receiving treatment. The results were better when the treatment was associated with a Monaldi aspiration. They were still better when the latter method and a Di Paola type of apico-axillary thoracoplasty were performed in conjunction with the intracavitary treatment. No untoward effects were noted during the treatment. The catheter was maintained in the cavity even during the surgical intervention. In view of the relatively small number of cases treated and the short period of observation, no statistical evaluation of the results is given.—*Sobre la nueva tecnica de estreptomicina endocavitataria en la cura de alguna forma de tuberculosis pulmonar cronica de predominante base biologica, A. Omodei Zorini & G. Botari, Rev. espan. de tuberc., May, 1949, No. 170: 327.*—(*L. Molnar*)

Thiosemicarbazone for Extrapulmonary Tuberculosis.—This is a preliminary report of 70 cases treated with thiosemicarbazone (TB 1/698) since August, 1948. The diagnosis of tuberculosis was supported in each case by radiologic evidence and, when possible, by bacteriologic and histologic findings. The chemotherapy was associated with all forms of approved treatment. Best results were obtained when the drug could be brought into direct contact with the tuberculous focus, such as skin and laryngeal lesions; or when the orally administered drug was eliminated through the intestines and the bladder which were sites of tuberculous lesions. Pre- and post-operative administration of the drug proved to be useful in preventing relapses and complications. Good results were obtained in tuberculous coxitis, mucosal tuberculosis, anal fistula, ulcers of the tongue, and empyema. In genital tuberculosis the results were poor in general. No effects were noted in tuberculous lymphadenitis. Since the margin between therapeutic and toxic doses is narrow, small doses are recommended. On the average, 0.15 gm. was given daily *per os*; for local treatment, 0.1 to 0.2 gm. in 10 to 20 cc. of physiological saline solution was used. The treatment was continued for several months. Liver damage was observed in a few cases and in the presence of this complication barbiturates were not well tolerated. The search for urobilinogen in the urine should be a routine procedure before the administration of thiosemicarbazone. Blood count and sedimentation should be checked every ten days.—*Zur Behandlung chirurgischer Tuberkulosen mit dem Thiosemicarbazon TB I 698, R. Hasche-Klünder & G. Leimbach, Deutsche med. Wchnschr., September 23, 1949, No. 38: 1135.*—(*L. Molnar*)

Experimental Chemotherapy of Tuberculosis.—The effect of various synthetic compounds against tuberculosis induced in mice by intravenous injections of virulent bacilli was studied. In previous experiments large doses of bacilli (0.75 mg.) were used; these produced necrotic pulmonary lesions. By reducing the dosage to 0.02 mg. of bacilli, progressive but less necrotic lesions were produced. Compounds previously found inactive were still inactive, with the exception of 4:4-diamino-diphenylsulfone which, under the new conditions, produced an unexpectedly good response, even better than that of *p*-aminosalicylic acid. A number of substituted members of the thiosemicarbazone series were found to have no effect against the lighter infection. Some favorable action was exerted in the present experiment by the thiosemicarbazones of *p*-nitro-benzaldehyde, *p*-methoxy-benzaldehyde, and *p*-hydroxy-benzaldehyde. Best results with a thiosemicarbazone came from the *p*-ethyl-sulfonyl-benzaldehyde derivative. This compound was more effective then the clinically applied *p*-acetyl-aminobenzaldehyde derivative of thiosemicarbazone.—*Studies in the chemotherapy of tuberculosis: Part VI. The comparison of some synthetic substances with streptomycin using mice infected with a light inoculum of Mycobacterium tuberculosis, E. Hoggarth, & A. R. Martin, Brit. J. Pharmacol., June, 1950, 5: 188.*—(*A. A. Cohen*).

Experimental Chemotherapy of Tuberculosis.—Approximately 1,000 compounds belonging to 11 chemical series were tested *in vitro* against tubercle bacilli over the past few

years by the authors. Twenty-four compounds with high *in vitro* activity were selected for testing in mice or guinea pigs, or both. None was judged active. The validity of various types of animal tests depends in large part on the range of variation of lesions in the controls.—*Experimental tuberculosis and its chemotherapy, B. Croshaw, & L. Dickinson, Brit. J. Pharmacol., June, 1950, 5: 178.—(A. A. Cohen)*

Citrinin and M. tuberculosis.—Citrinin is an antibiotic which appears to have *in vitro* activity against human, bovine, and avian types of *M. tuberculosis*. With human-type tubercle bacilli, citrinin at 10 γ per cc. produced doubtful effects, and at over 100 γ very marked inhibition of cell multiplication. The local strain No. 49 was more sensitive than the standard strain H37Rv. The addition of 10 per cent human plasma did not lower the bacteriostatic activity of citrinin significantly.—*The effect of citrinin in vitro on Mycobacterium tuberculosis, Y. Wang & C. W. Chia, Chinese M. J., November, 1949, 67: 612.—(B. Hyde)*

LABORATORY STUDIES

Tubercle Bacilli and Leukocyte Migration.—Tubercle bacilli are rapidly phagocytized by polymorphonuclear leukocytes which characteristically clump, apparently as a result of engulfing the bacilli. In mice, injected avirulent tubercle bacilli are removed from the peritoneal cavity more rapidly than the virulent forms. Virulent bacilli added to tissue cultures of the buffy coat of guinea pig blood markedly inhibit the migration of the polymorphonuclear cells. The present paper deals chiefly with this inhibition of migration in a slide cell so designed that the rate of migration of leukocytes could be easily followed and measured. This cell consisted of a microscope slide and a long coverslip separated only by a U-shaped piece of filter paper and sealed with paraffin. Heparinized blood, with or without tubercle bacilli, was introduced into the cell by capillary attraction. After filling, the slide was sealed and gently centrifuged to separate the red cells, leukocytes, and plasma. On incubation the plasma quickly clotted and the migration of the leukocytes forming the buffy coat could be observed under the microscope. This migration was inhibited by virulent tubercle bacilli pathogenic for the class of animal (mammal or bird) from which the leukocytes were obtained; it was not affected by the avirulent variants of these microorganisms nor by bacilli pathogenic for animals of the other class. Thus, the inhibition appeared to be related to pathogenicity. There was no indication that the viability of polymorphonuclear leukocytes was affected by prior engulfment of tubercle bacilli; their uptake of oxygen and ability to destroy pneumococci were unaltered. The only alteration, other than the change in the rate of migration, observed in leukocytes that had engulfed virulent tubercle bacilli was their increased tendency to adhere to other leukocytes as if the cell surface had become sticky. The depression of migratory activity may have been due to such a change in the surface properties of the leukocytes: the bacilli themselves did not seem to have any really toxic effect.—*The effect of tubercle bacilli on the polymorphonuclear leukocytes of normal animals, S. P. Martin, C. H. Pierce, G. Middlebrook, and R. J. Dubos, J. Exper. Med., April 1, 1950, 91: 381.—(J. S. Woolley)*

Tuberculosis in Mice.—The author produced a progressive pulmonary infection in mice by an intravenous inoculation with virulent and relatively avirulent human tubercle bacilli. Mice infected with 0.75 mg. of virulent bacilli died with necrotic lesions in the lungs within three weeks. When mice were inoculated with smaller doses of virulent or larger doses of the avirulent strains of *M. tuberculosis hominis* a longer survival time was noted. Also proliferative rather than necrotic lesions were produced. Mice previously vaccinated with living tubercle bacilli were more resistant to reinfection. This resistance was expressed by the formation of proliferative lesions and longer survival time, but not by fibrocaseous lesions or remission of the disease.—*The patho-*

genesis of tuberculosis in mice infected intravenously with human tubercle bacilli: The use of mice in chemotherapeutic tests, G. T. Stewart, Brit. J. Exper. Path., February, 1950, 31: 5.—(H. J. Henderson)

Mycobacterium from Gia.—What may be a new acid-fast bacillus (*"Mycobacterium giae"*) was isolated from sick specimens of an edible, fresh-water toad, the gia (*Leptodactylus pentadactylus*) collected near Bahia, Brazil. The microorganisms produced yellowish, dry colonies on egg medium and fermented only glucose and arabinose. They were nonpathogenic for rodents but produced a nodular infection of the liver in lizards. Naturally infected toads were feeble and emaciated, with many nodules in the liver, lungs, peritoneum, intestines, and joints. These nodules were discrete, caseated, and surrounded by a fibrotic tissue; they contained acid-fast bacilli. Acid-fast bacilli producing colonies like those of *"M. giae"* were isolated from the water in which the toads live.—*Tuberculose das Gias (Leptodactylus pentadactylus), E. Darzins, Arq. brasil da Tuberculose, 1950, 9: 29.—(L. B. Hobson)*

Vascular Pressures in Emphysema.—A significant elevation of pulmonary arterial diastolic pressure was found in 24 patients with chronic pulmonary emphysema. Systolic pressure was elevated also in the majority of these patients. Evidence is presented which indicates that pulmonary hypertension in emphysema is related to an increased vascular resistance in the lungs. Marked respiratory variation is the outstanding characteristic of intravascular and intracardiac pressure records in patients with emphysema. This depends upon abnormally wide fluctuations in intrathoracic pressure. There is no correlation between the degree of pulmonary hypertension and the severity of the emphysema as estimated by the altered ratio of residual air to total lung volume. Eight of the 24 patients with emphysema had definite evidence of right heart failure prior to study. The pulmonary arterial pressure was significantly higher and the oxygen saturation of the arterial blood was significantly lower in this group than in the group of 16 patients with emphysema uncomplicated by right heart failure. The mean arteriovenous oxygen difference in 23 patients with pulmonary emphysema was similar to that reported for normal subjects. No evidence was found to indicate that oxygen unsaturation of the arterial blood in emphysema induces an increase in the output of the heart (Authors' summary).—*Pulmonary hypertension in chronic pulmonary emphysema, C. W. Borden, R. H. Wilson, R. V. Ebert, & H. S. Wells, Am. J. Med., June, 1950, 8: 701.—(T. H. Noehren)*

Compression and Decompression.—Rapid compression of anesthetized dogs to 4.5 or 9 atmospheres caused a pronounced increase in the alveolar carbon dioxide. This may have resulted from blocking the expiration of alveolar air and from forcing air in the dead space and alveoli into the periphery of the lung before alveolar mixing of air was completed. These changes temporarily diminished and in some cases reversed the normal alveolar carbon dioxide diffusion gradient so that carbon dioxide was driven back into the blood; the gradient for oxygen was augmented and hyperoxic-hypercapnia resulted. Rapid decompression caused a sharp initial decrease in the alveolar carbon dioxide below the value before compression frequently followed by a temporary elevation. This decrease may have been due to a forced expiration of alveolar air so that the carbon dioxide diffusion gradient from the blood to the alveoli was sharply increased. The inspiration of oxygen was blocked and the oxygen diffusion gradient between alveoli and blood was reversed. Hypocapneic-anoxia resulted. The rapidity of the pressure changes was important in establishing these abnormal states. The changes in the carbon dioxide content of the alveoli, blood, and tissues seem to explain the subjective and neuromuscular reactions induced by rapid compression; there is no evidence that "nitrogen narcosis" plays any role. Some of the responses to rapid decompression commonly attributed to aero-embolism and to decreased

oxygen tension may be due to decreased inhalation, to sudden withdrawal of oxygen already present in the alveoli, and to acapnia. The sudden withdrawal of gases from the pulmonary blood may explain the cardiac effects reported as attending explosive decompressions.—*Tensional changes of alveolar gas in reactions to rapid compression and decompression and question of nitrogen narcosis, J. W. Bean, Am. J. Physiol., June 1, 1950, 161: 417.*—(*G. C. Leiner*)

Fluoride and Beryllium Toxicity.—The potentially toxic dusts or vapors encountered in industrial processes are frequently not single compounds but mixtures of various substances. An example is provided in the manufacture of beryllium in which hydrogen fluoride or other fluorides have been shown not only to be present but actually to exist in amounts several hundredfold greater than that of beryllium. Moreover, clinical disease has occurred among plant personnel at sites where these mixed exposures existed. Hydrogen fluoride vapor inhaled by rats at a concentration of 8 mg. per cubic meter produced a twofold enhancement of the toxicity of a soluble beryllium salt inhaled by these rats. A beryllium salt inhaled as a mist at 9 mg. per cubic meter alternately with hydrogen fluoride increased the deposition of fluoride in tooth and bone to 1.3 times that obtained with the inhalation of similar quantities of hydrogen fluoride vapor alone at 8 mg. per cubic meter.—*Acute inhalation toxicity of beryllium: II. The enhancing effect of the inhalation of hydrogen fluoride vapor on beryllium sulfate poisoning in animals, H. E. Stokinger, N. J. Ashenburg, J. DeVoldre, J. K. Scott, & F. A. Smith, Arch. Indust. Hyg. & Occup. Med., April, 1950, 1: 398.*—(*T. H. Noehren*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Tuberculosis Statistics.—Investigations were carried out on the following groups in Norway: (*1*) 889 persons whose conversion on tuberculin testing was recorded within a limited interval of time (less than two years in 75 per cent of the cases); (*2*) 439 persons with a positive tuberculin reaction before they were twelve years old; (*3*) 818 persons with hilar adenitis, 31 per cent having a record of tuberculin conversion. These persons had been under observation for periods as long as seventeen years after the presumptive primary infection. Answers were sought to 3 questions: (a) What proportion of persons with a primary infection develop tuberculous disease sooner or later, and how many of them die of it? (b) How long is the interval between infection and demonstrable disease or death? (c) What is the morbidity or mortality in special groups of persons contracting a primary infection when compared with primarily infected persons as a whole? Erythema nodosum occurred during the first year after infection in 5 to 10 per cent of patients, most frequently in females and comparatively rarely in males after the age of fifteen years. The frequency of hilar adenitis after a primary infection seemed to diminish as the age at the time of infection rose. It followed infection immediately in 60 per cent of the children infected before three years of age, in 40 to 50 per cent of those infected in the age group four to twelve years, in 25 per cent in the age group thirteen to nineteen years, and in 20 per cent of the adults. A pulmonary infiltration was radiologically demonstrated in 20 to 25 per cent of the infected persons in all of the age groups; it was relatively more frequent among the primarily infected persons with hilar adenitis. Exudative pleuritis nearly always occurred in the first observation year after infection at all ages; it developed in about 3 per cent of those whose primary infection occurred before the age of thirteen years, and in 7 to 8 per cent of those whose primary infection occurred after this age. No sex difference was noted, but it was more frequent in primary infection with hilar adenitis. The annual tuberculosis morbidity after infection in childhood was about 0.3 per cent during the years immediately after infection. It remained at about the same level in subsequent years, provided the persons infected had passed the age of thirteen years. The total morbidity after infection in childhood was 2 to 3 per cent.

When a primary infection occurred after the age of thirteen years, the subsequent annual morbidity during the first three to four years was 2 to 3 per cent. After the third observation year, the annual morbidity fell and was under one per cent. Such a morbidity rate probably persisted for a long period after infection though with a continuing fall. Thus the total morbidity for this age on infection was over 10 per cent. The morbidity findings were confirmed by the mortality findings. When infection occurred in the age group up to three years, the total mortality was about 3 per cent, chiefly due to meningitis. When infection occurred in the age group four to twelve years, the total mortality of one per cent was spread over a long period and resulted mainly from extrathoracic tuberculosis in the early observation years. In the late observation years, when adolescence had been reached, it was due to pulmonary tuberculosis. When infection occurred after the age of thirteen years, the total mortality was about 5 per cent and was due chiefly to pulmonary tuberculosis. It was somewhat higher when infection occurred between the ages of thirteen and nineteen years than later on and was higher among those with associated hilar adenitis. The total mortality, more evenly distributed over a long observation period than the morbidity, was about 0.5 per cent per observation year but reached a peak of one per cent in the third observation year. The morbidity and mortality were highest among those with a family history of tuberculosis. A high sedimentation rate in the first half year after infection meant a definitely higher morbidity and mortality rate from pulmonary tuberculosis. This was particularly the case when infection had occurred after the age of thirteen years. The demonstration of tubercle bacilli during the first half year after infection also meant a somewhat higher pulmonary tuberculosis morbidity and mortality but only during the early observation years. The appearance of erythema nodosum did not affect the morbidity rate. A visible pulmonary infiltration (primary focus), however, considerably increased the pulmonary tuberculosis risk during the first four observation years and also gave a higher mortality, as did pleuritis developing during the first observation year. Finally, extrathoracic tuberculosis usually occurred during the first two or three years after infection. Its total morbidity was 5 to 10 per cent after infection in the age group up to three years and thereafter it was about 2 per cent in all the later ages. After the age of thirteen years it was relatively more frequent among those with hilar adenitis.—*Statistical investigations of the relationship of tuberculosis morbidity and mortality to infection, S. N. Meyer, Acta tuberc. Scandinav., 1949, Supplement 18.*—(*K. T. Bird*)

Indian Tuberculosis Program.—In 1925 the death rate among American Indians was seven times that of the general population. Because of the low socioeconomic status of the Indians, the varied cultures, the ethnic differences, the nomadic life of some tribes, and language barriers, it is necessary that the personnel be better trained and more experienced in order to carry on the tuberculosis control program. The first method in the program is case finding by roentgenographic microfilms; the second is to obtain routine chest roentgenograms of all hospital and clinic admissions. A third method is to examine roentgenographically all employees of the Health Division upon their entry in the Indian Service and annually thereafter. The fourth and fifth methods are hospitalization of the discovered cases of tuberculosis and follow-up of the patients after hospitalization. The sixth procedure is administration of BCG vaccine to all children in Indian Service boarding schools and adjacent mission schools. During the period 1935–1938, approximately 1,500 children were vaccinated. In 1949 alone, more than 13,000 Indian children were vaccinated with BCG. The seventh method is the integration of Indian Bureau activities with other governmental and nongovernmental agencies wherever possible. The eighth method depends upon the application of state, county, and city health laws and regulations to each reservation so that uniformity of methods may

be used in providing adequate control of communicable diseases. The ninth and most important technique used is that of health education. The control of tuberculosis among Indians is possible, using time-tested public health and sanatorium procedures. Operating funds and personnel must be provided to establish: first, continuity of the program at the level of a well-organized and operated rural county health department; and, second, adequate sanatorium beds for cases found to require treatment.—*Tuberculosis control among American Indians, H. DeLien & A. W. Dahlstrom, Lancet, April, 1950,* ***70:*** *131.—(H. J. Henderson)*

Tuberculin Skin Testing.—In a previous study involving 2,152 undergraduate students, the authors reported that satisfactory and comparable results could be obtained by using Vollmer patch testing where its use is desirable instead of the two-dose intradermal PPD test for tuberculosis. In the fall of 1948 they verified their results of the previous study by retesting a second group of 2,546 students. Readings made at the end of 48 hours when the patch was removed were compared with the result at the end of 96 hours. Fifty per cent of the final positives were read as negative at 48 hours, emphasizing the great importance of the 96-hour reading.—*Further comparative studies in tuberculin skin testing among 2,500 students, E. S. Krug & H. R. Glenn, Lancet, April, 1950,* ***1:*** *139.—(H. J. Henderson)*

Tuberculosis in Old Age.—Pulmonary tuberculosis, and particularly pulmonary tuberculosis with positive sputum, is by no means restricted to young adults. Pulmonary tuberculosis can and does occur in an early stage in the older age group. The maximum incidence of tuberculosis morbidity and mortality, particularly in men, is slowly shifting from the young adult to the middle age group. In a 200-bed tuberculosis hospital, 22 per cent of the patients were found to be over 50 years of age. Active, sputum-positive tuberculosis was present and was discovered after the age of 50 in 19 per cent. Only a few presented chest symptoms which led to their diagnosis. The majority had been diagnosed by routine roentgenograms. The average age at the time of diagnosis was 57.6 years.—*Pulmonary tuberculosis in the older age groups, A. D. Temple & E. F. Crutchlow, Canad. M. A. J., June, 1950,* ***62:*** *565.—(T. H. Noehren)*

Rehabilitation.—In a program of rehabilitation within a sanatorium a committee composed of the directors of social service, education, and occupational therapy, the librarians, the physician in charge of the case, and the rehabilitation counselor meets regularly. They discuss the means of assisting the individual patient to utilize his physical, social, and economic capacities to the fullest extent. This meeting is held as soon after admission of the patient to the hospital as adequate information is available. The physician gives the diagnosis and prognosis, the probable length of stay in the hospital, the type and amount of activity to be permitted, and an estimate of the eventual working capacity. The social service worker reports on the social picture of the patient and the family and discusses previous education and employment. The librarian and occupational therapist present any knowledge they may have acquired about the patient. The rehabilitation counselor describes the patient's former occupation and asks the physician's opinion as to the advisability of the patient returning to his previous employment. General recommendations are then made as to the type of program to be followed. The rehabilitation counselor directs and integrates the efforts of the other departments that emphasize bedside or ambulatory teaching and training. She also coordinates the inpatient and ex-patient program.—*A modern program of rehabilitation for the tuberculous, L. S. Cohen & M. L. Boice, Lancet, April, 1950,* ***1:*** *137.—(H. J. Henderson)*

Neighborhood Beryliosis.—The term "delayed chemical pneumonitis" has been coined to describe cases of chronic pulmonary disease

occurring in workers exposed to beryllium compounds. In the 3 case histories presented with autopsy findings, the findings were similar to delayed chemical pneumonitis but the patients never were employed in a beryllium plant. The first patient lived approximately two blocks from the plant until twenty months before her death, when she lived one and one-half miles away. The second patient lived at places one-half to three miles from the beryllium plant within the ten years prior to her death. The third case was that of an eight-year-old child who lived approximately one mile east of the beryllium plant until fifteen months before she showed symptoms of pulmonary disease. She moved out of town eighteen months before she had any symptoms of pneumonitis. Her father and uncle had been employed in the beryllium plant in the previous years. These 3 cases are part of an original series in which the exposure to beryllium was no more direct than that incurred by living in the neighborhood of a fluorescent lamp plant.—*Chronic pulmonary granulomatosis in residents of a community near a beryllium plant: Three autopsied cases, C. Chesner, Ann. Int. Med., June, 1950,* ***32:*** *1028.*—(*T. H. Nochren*)

Silica and Alumina Solubility.—The theory of silicosis which postulates that silica must be in a soluble form in order to produce its well-known tissue response has led to an intensive study of the effects of alumina and silica on each other. In general, the rate of dissolution of silica varies in an inverse ratio to the particle size. No such relationship is observed in the case of alumina. In general, the forms of alumina which are most active in depressing the solubility of silica are the ones whose own solubilities are the least affected by the action of silica. Similarly, the types of silica which are the most active in depressing the solubility of alumina are the ones whose own solubility is least affected by the action of alumina. Black aluminum powder and xH1010 alumina, which are used at present for therapeutic purposes, are among the most active forms of alumina in their ability to depress the solubility of silica. Alumina fumes given off in electric furnace operations will reduce the solubility of many types of silica to low levels.—*Solubility of silica and alumina, C. M. Jephcott & J. H. Johnston, Arch. Indust. Hyg. & Occup. Med., March, 1950,* ***1:*** *323.*—(*T. H. Nochren*)

Latent Silicosis.—A case of silicosis is presented illustrating the development of roentgenographic evidence of the disease four years after exposure to silica. A normal chest radiograph was demonstrated at the time of the patient's separation from employment. It is suggested that yearly chest roentgenograms should be made for several years following separation from any employment which involves a significant exposure to silica dust.—*Latent silicosis, M. McQuitty, B. Cuddihy, C. A. MacIntosh, & G. T Adams, Canad. M. A. J., July, 1950,* ***63:*** *69.*—(*T. H. Nochren*)

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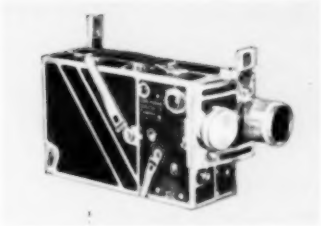

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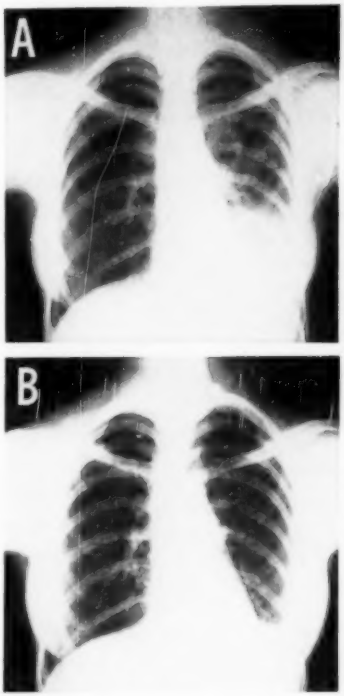

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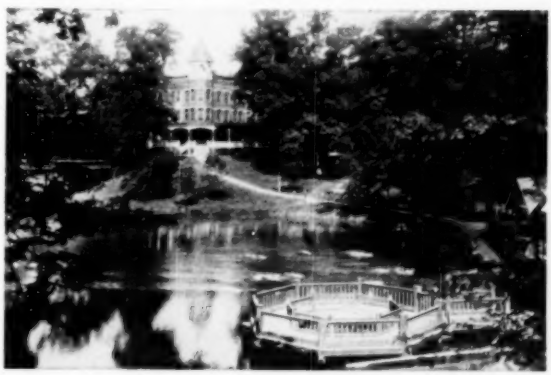

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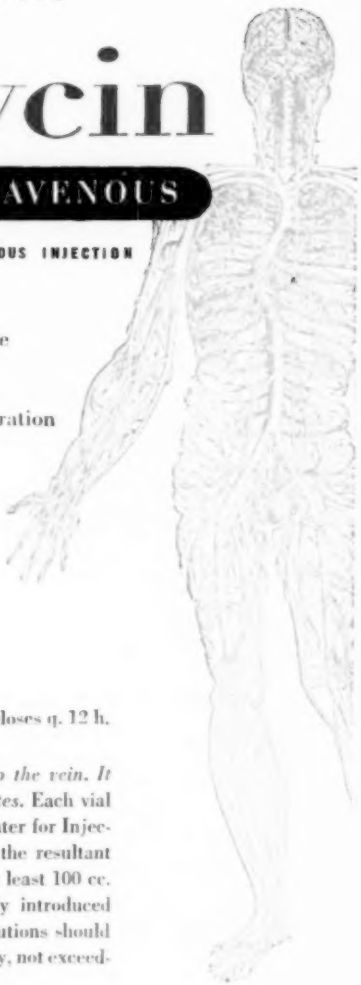

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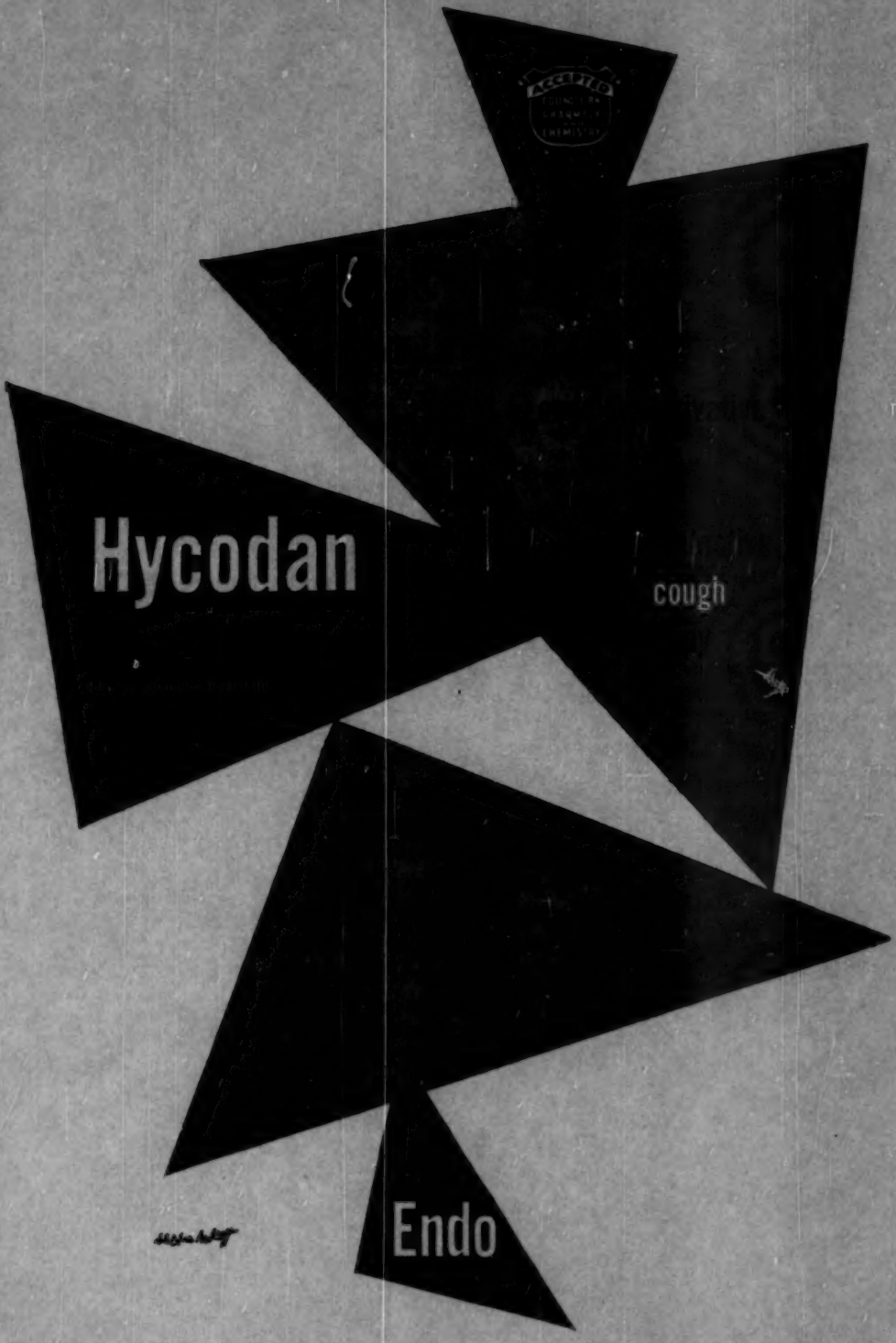
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